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HANDBOOK OF PHYSIOLOGY

SECTION 2: Circulation, VOLUME II

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HANDBOOK OF PHYSIOLOGY

*A critical, comprehensive presentation
of physiological knowledge and concepts*

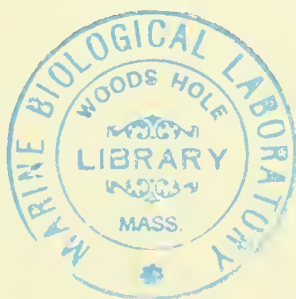
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NOTE: For coverage of blood flow to the brain, see "The Cerebral Circulation" by S. S. Kety, chapter LXXI, pp. 1751-1760, Neurophysiology section of the *Handbook* series.

Functional anatomy of cardiac pumping¹

GERHARD A. BRECHER
PIERRE M. GALLETTI

*Department of Physiology, Emory University
School of Medicine, Atlanta, Georgia*

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ALTHOUGH THE PURELY MECHANICAL NATURE of cardiac pumping is taken for granted by modern scientists, this view has not always been accepted in the past. Only during the last hundred years were the forces of muscle contraction finally stripped of the 'vis vitalis' and ascribed exclusively to energy transformation according to the laws of physics and chemistry. In this historical process, the heart which had been formerly thought of as the seat of emotions, was deprived of all metaphysical connotations and became an organ of purely mechanical function just

as the skeletal muscle. It is of interest to trace briefly the emergence of this concept (160, 161).

During the age of the pyramids (3000–2500 B.C.) an unknown Egyptian clearly recognized the heart as the center of a system of distributing vessels and associated the pulse with the cardiac beat. The Greek philosopher Alcmaeon of Croton (about 500 B.C.) distinguished the veins from the arteries and asserted that the seat of sensation was not in the heart but in the brain. The function of the heart as a pump was apparently expressed for the first time by Plato (427–347 B.C.) when he stated: it "pumps particles as from a fountain into the channels of the veins, and makes the stream of the veins flow through the body as through a conduit." Hippocrates (493–423 B.C.) had described the cardiac valves, the ventricles and the great vessels, but he did not refer to the pumping action, which he might have taken for granted. For Aristotle (384–322 B.C.) the heart was the seat of "innate heat" and also of the soul. This notion was probably based on the observation that death results from dissection of the beating heart. However, from his studies on the embryonic chick heart Aristotle may have had knowledge of the pumping function. Erasistratus (310–250 B.C.), who described the aortic valves, pulmonary valves, and chordae tendinae, and Galen of Pergamon (131–201 A.D.) both stated that the heart is a pressure-suction pump. Their view was founded mainly on the assumption that during diastole blood was sucked into the ventricles by active enlargement of the cardiac walls [discussed by Ebstein (40), Böhme (14)]. They also believed that blood is expelled backward into the caval veins during ventricular systole. The first definite statement concerning the continued forward flow of blood from the right ventricle through the lungs into the left heart was made by Ibn an-Nafis (1210–1299 A.D.). The first scientist of the Renais-

¹ The results of some recent experiments of the authors and their colleagues are quoted in this paper. This work was supported in part by USPHS grant H-3796, and grants from the Life Insurance Medical Research Fund and the Georgia Heart Association.

sance who recognized the heart as a hollow muscle and probably as a pump was the artist-engineer, Leonardo da Vinci (1452–1519 A.D.), who stated: “The heart is a principal muscle, in respect of force, and it is much more powerful than the other muscles” [Keele (90)]. However, it remained to William Harvey (1578–1657) to prove that the heart, and not the liver, is the center of the vascular system and that it propels the blood unidirectionally by its rhythmical contractions as would the repeated strokes of a man-made pump. The microscopic proof of the muscular nature of the heart was brought by Niels Stenson (1638–1686), who demonstrated that the substance of the heart is composed of fibers, membranes, arteries, veins, and nerves just as is the substance of other muscles. Once this important point had been firmly established, it became customary to consider the heart as a pump, to develop analogies with mechanical systems of fluid transfer, and to apply to the myocardium the increasing knowledge about skeletal muscle contraction. The present chapter is a rather general and classically oriented treatment of the mechanical function of the heart. It attempts to provide an understanding of the anatomical structures, while avoiding teleological oversimplification as well as useless controversies about functions.

The role of the heart consists of providing the body tissues with a continuous stream of blood. The heart fulfills this function by converting potential energy (primarily chemical energy, secondarily energy of position) into kinetic energy, as movement is imparted to the blood ejected from the ventricular cavities. From the standpoint of cellular function at large, it does not matter whether tissue perfusion is brought about by alternate contraction and relaxation of myocardial cells, or by the action of an artificial pump. This concept has been established on a firm experimental basis by the advent of extracorporeal circulation techniques, whereby a mechanical pump substituted for the human heart can fully support the circulation. Thus the heart can be looked upon as a pump inserted in the circulatory system and its function can be described by analogy with purely mechanical systems.

Mechanical pumps are divided into two main classes: kinetic pumps and positive displacement pumps. In the former class, kinetic energy is added to the fluid by the forced rotation of an impeller (fig. 1A). In the latter class, the fluid is progressively displaced from a suction inlet to a discharge opening. Two kinds of positive displacement pumps need to

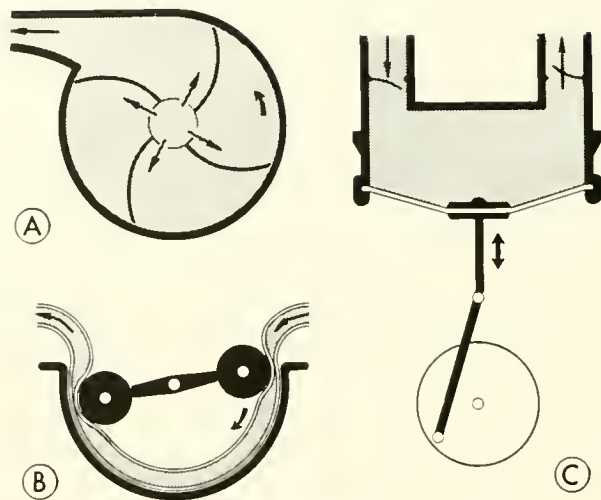


FIG. 1. Mechanical analogues for some pumping principles embodied in the heart. A: kinetic pump in which energy is added to the fluid by the rotation of an impeller. B: rotary pump in which fluid is propelled through squeezing a resilient tube by means of rollers mounted on a rotating arm. C: reciprocating pump in which fluid is displaced by the back and forth movement of a diaphragm while valves give direction to the stream.

be mentioned here. In rotary pumps (fig. 1B), moving members trap a portion of the fluid in a chamber of pliable tubing and conduct it toward the outlet. The segment of tubing occluded acts as a valve to prevent backflow. In reciprocating pumps (fig. 1C) a cavity limited by two valves is subjected to the action of a piston or diaphragm. As the piston moves back and forth, fluid is drawn in through the suction valve and forced out through the discharge valve.

The action of the heart in some invertebrates can be compared to that of rotary pumps, since forward movement of fluid is obtained by peristaltic movements of the walls. In the mammalian heart also some degree of blood propulsion may be accomplished on the “progressive cavity principle” as in rotary pumps, particularly the displacement caused by the wringing action of the ventricles. However, cardiac action in vertebrates most closely resembles that of reciprocating pumps. It is characterized by pulsatile action, by the presence of valves, and by the capability of the pump to be adjusted in terms of either speed, or volume displacement, or of speed and volume displacement simultaneously. Although the design of the heart has nothing in common with that of kinetic (centrifugal) pumps, its control displays two characteristics for which kinetic pumps are appreciated in technology: namely that the volume

output is directly related to the input pressure, and is inversely related to the pressure head against which the pump works. Like centrifugal pumps, the heart has the tendency to deliver a higher flow as more blood is fed into it at the atrial level; it also provides a lower flow when the resistance to ejection in the vascular system increases.

A close look at mechanical pumps for cardiac substitution throws a light on built-in features of the natural heart that one easily takes for granted. Adequate perfusion of an adult human organism under all possible conditions requires that:

- 1) The heart be able to move blood volumes ranging from 3 to 30 liters per min and to pump against pressures up to 300 mm Hg.
- 2) Even at maximal cardiac output, the flow velocity must not exceed the limit of tolerance for mechanical trauma to blood corpuscles through turbulence, friction, or cavitation (1-2 m/sec).
- 3) The relationship between stroke volume and stroke rate must not deviate much from an optimum which is set by the elastic properties of the cardiac walls, the time needed for efficient transformation of potential into kinetic energy and by the lowest flow velocity compatible with the output required.
- 4) The valves must easily open during their flow phase, yet be competent and prevent regurgitation of blood during their holding period.
- 5) The regulation of the pumping action must be automatically controlled through sensing elements with feedback mechanisms which adapt the output to the tissue demands [see also Wagner (153)]. These control mechanisms must integrate hemodynamic data (e.g., perfusion flow, arterial and venous pressures) and metabolic data (e.g., arteriovenous oxygen difference) to maintain viable conditions.

Considering these points in more detail, one must first emphasize the pumping capacity of the heart. As 3 to 30 liters per min of blood is pumped by the left ventricle into the systemic circulation, practically the same amount is ejected by the right ventricle into the pulmonary vascular bed. Furthermore, the atria have some pumping function of their own, so that the combined pumping of all the chambers of the human heart is in the order of 7 to 70 liters per min, depending upon the state of muscular activity. A range of this magnitude (1:10) is not easily obtained in artificial pumps and, when it is reached, it is at the price of considerable sacrifices in mechanical efficiency (ratio of work produced to fuel consumed). On the contrary, the mechanical efficiency of the heart does not seem to be very closely related to cardiac output.

The extended scale of activity over which the heart can perform is certainly facilitated by the elastoviscous properties of the cardiac walls. The cavities are distensible over a wide range of volume increments without much increase in intraventricular or intra-atrial pressures [see fig. 2, and Little (99)]. Therefore the heart can easily accommodate and deliver varying stroke volumes even if the stroke frequency remains unchanged. Furthermore the time needed for the transformation of chemical into mechanical energy apparently comprises only a fraction of the systole. At a constant stroke volume the heart can increase its minute output simply by beating faster and shortening the pause between the strokes without affecting the energy conversion processes. The limiting factor of cardiac output at high heart rates is not an encroachment on the time needed for energy conversion but an encroachment on the time needed for filling the pump chambers (ventricular filling phase).

Another fundamental difference between artificial pumps and the heart is that in the former a force is applied from the outside to activate a part or the entire wall of the pump chamber, whereas in the latter the force is developed within the wall of the pump chamber itself by small elements, the muscle fibrils, which alternately shorten and lengthen. Furthermore, since the heart is surrounded by other resilient structures in the thorax, there is an interaction of the physical forces developed in the myocardium and those developed either passively or actively in these structures [Pfuhl (129, 130), Blair & Wedd (12)]. For example, during ventricular contraction and ejection the elastic forces of the lungs oppose to a small extent the diminution of the ventricular size, whereas during ventricular relaxation the same forces of the lungs enhance slightly the expansion of the ventricles. These forces are said to be negligible as compared with the intravenous filling pressures (60, 64). Mechanical effects are exerted upon the rhythmical form changes of the heart by such structures as the pericardium, the attachments of the heart to the large vessels, the sternum, the mediastinal tissues, and the diaphragm through its changes in position during respiration or because of varying degrees of abdominal filling. The complexity of these forces, in terms of direction and magnitude, and their continuous changes during the cardiac and the respiratory cycle make it presently impossible to evaluate quantitatively the contribution of extracardiac structures to cardiac pumping. Nevertheless, their importance is demonstrated by the possibility of pumping blood solely by the action

of external forces on the heart [Hosler (81), Stephenson (150)]. In closed-chest cardiac massage, vigorous pressure on the lower part of the sternum causes ejection of the ventricular content into the large arteries. Conversely, when pressure is released, the recoil is sufficient to permit the venous pressure to fill the ventricles again [Kouwenhoven *et al.* (92)]. In this manner, a sufficient, though subnormal, cardiac output can be maintained in the absence of any myocardial activity. This points again to the fact that, in principle, it does not matter whether the propulsion of blood through the body is brought about by the contraction of cardiac fibers or by any other suitable forces applied to the blood contained in the ventricles.

MACROSCOPIC STRUCTURES

A great deal of commonly accepted knowledge about cardiac pumping is derived from purely morphological considerations. Although conclusions reached in this manner have occasionally proved to be correct, morphological reasoning often leads to fallacious functional interpretations of structural findings. In the case of the heart, physical vector analysis of all the mechanical forces involved is especially difficult because of the great complexity of the anatomical structures and of the perplexing geometry of cardiac filling and emptying. We have only a limited knowledge of the sequence of events as they occur during muscular contraction and relaxation within various parts of the myocardium. In this particular section an attempt is made to describe the macroscopic structures of the heart with reference to their probable function as deduced from the anatomical observations. A topographic anatomical description of the heart is available in standard texts (51, 95, 98, 101).

Composition of Cardiac Tissues

The myocardium is the most important structure of the heart because its contraction causes the blood to flow. However, it should be realized that only part of the cardiac walls consists of muscle fibers, and that within the muscle fibers, the contractile substance is limited to the fibrils. Indeed about half of the heart's weight is made of noncontractile material such as the sarcolemma in the muscle fibers, connective tissue in the heart skeleton, tendons and valves, and finally blood vessels, lymphatics, and nerve fibers. All these elements are interwoven with

the muscle fibers or closely connected to them (45, 59). During cardiac contraction or relaxation, they are deformed and resist to some degree the shortening or lengthening of the myofibrils.

Little is known about the mechanical effects of the coronary vessels upon the function of the ventricles. Though relatively inconspicuous in a "dead" heart, they appear heavily engorged with blood in the live organ. In fact, since 5 to 10 per cent of the cardiac output passes through the coronary system, a significant mass of the beating heart consists of circulating blood contained within the anatomical bounds of the epicardium. During heavy exercise the coronary blood supply is probably so great that one might look upon the myocardium as a spongy structure of muscle fibers suspended like chains of islands in a lake of blood. In the past it has been postulated frequently that the degree of filling of the coronary vascular bed affects in some form the ventricular contraction.

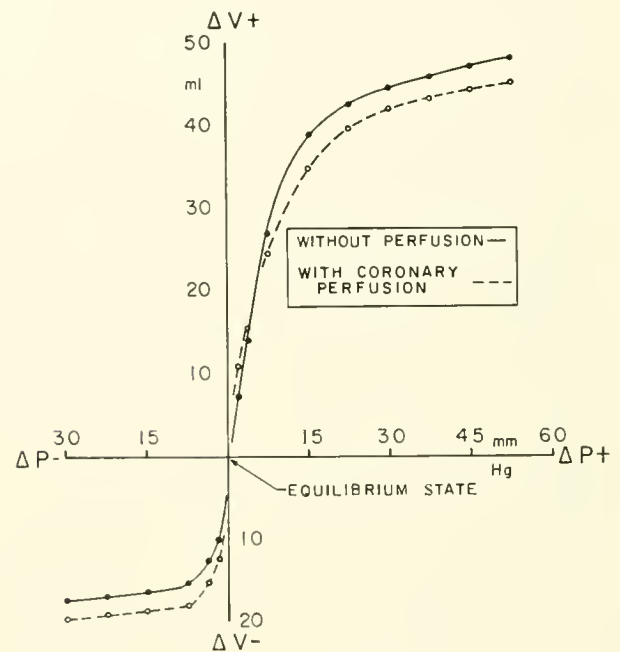


FIG. 2. Left ventricular pressure-volumes curves of a dog heart illustrating the changes resulting from coronary perfusion. The freshly excised heart of a 13.5-kg dog was submerged in Locke's solution and assumed its elastic equilibrium state (zero transmural pressure, origin of the coordinates) upon cessation of spontaneous contraction. The curves were obtained by addition or reduction of the intraventricular volume [Brecher & Kissen (22)]. The origins of the coordinates for the perfused and unperfused heart were arbitrarily superimposed. At negative (and up to +5 mm Hg) intraventricular pressures the ventricle accommodated a greater volume with coronary perfusion than without. At pressures above +5 mm Hg the ventricle accommodated less fluid with coronary perfusion than without (Horres *et al.*, unpublished data).

Most of these postulates were of speculative nature. For example, Donders (39) stated that "the blood which enters at the end of systole into the coronary arteries seems to cause a slight active expansion of the heart, especially of the ventricles." This view was originally formulated in 1855 by Brücke (26) and also advocated by Luciani (102). Based on X-ray kymograph studies, a modern modification of the same hypothesis was presented by Cignolini (34) without conclusive evidence. However, recent work by Salisbury *et al.* (141) indicates that the filling of the coronary bed affects the ventricular distensibility. There are indeed significant differences in the ventricular pressure volume relationship depending upon whether the coronaries are perfused or not [Brecher *et al.* (24)]. In figure 2 the S-shaped pressure volume curve of the ventricle with an empty coronary bed (solid line) is different from that obtained during coronary perfusion (broken line). This shift of the curve when the coronary bed is perfused indicates that the perfused heart accommodates more fluid at low intraventricular pressures and less fluid at high intraventricular pressures. Around the elastic equilibrium state (zero transmural pressure) the perfused heart is somewhat stiffer than the nonperfused heart. The effect of varying degrees of engorgement of the coronary bed upon the distensibility of the beating ventricle during the different phases of the cardiac cycle is still unknown.

The heart skeleton, the chordae tendineae, and the cells of the Purkinje system are noncontractile, yet are functional components of the myocardium. The heart skeleton (fig. 3) is represented by four interconnected fibrous rings of dense connective tissue, which surround the orifices of the great vessels. The musculature of the ventricles and atria, the roots of the large vessels, and the heart valves are attached to this skeleton, which also anchors the tendinous endings of the ventricular muscle (see below). An important function of the cardiac skeleton is to provide a firm basis for the attachment of the cardiac valves. Another function, though less frequently mentioned, is to aid in keeping the orifices open during the phases of blood inflow and outflow. During ventricular activity, the orifices undergo changes in form which probably involve also the cardiac skeleton as indicated in the different outlines of the orifices during systole and diastole in figures 4, 5, and 6. By inserting a finger through the atrial appendage in the intact beating heart, one can easily verify that the atrioventricular valve rings become smaller during ventricular contraction and larger during relaxation. This observation, which has not been substantiated by precise measurements as yet, indicates that the fibrous tissues of the heart skeleton are passively deformed by myocardial contraction and thereby store energy which is released

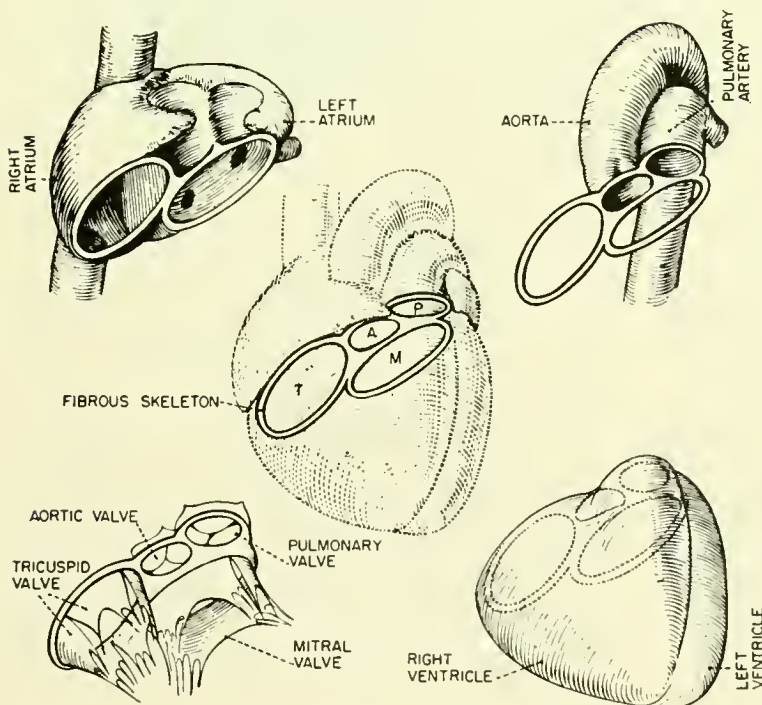


FIG. 3. Anatomic components of the heart depicting the relation of the fibrous skeleton to the heart chambers and arterial roots. The trunks of the aorta and pulmonary artery as well as the atria are fastened to the cranial aspect of the four annuli fibrosi, whereas the ventricles are attached to the caudal aspect. [From Rushmer (139).]

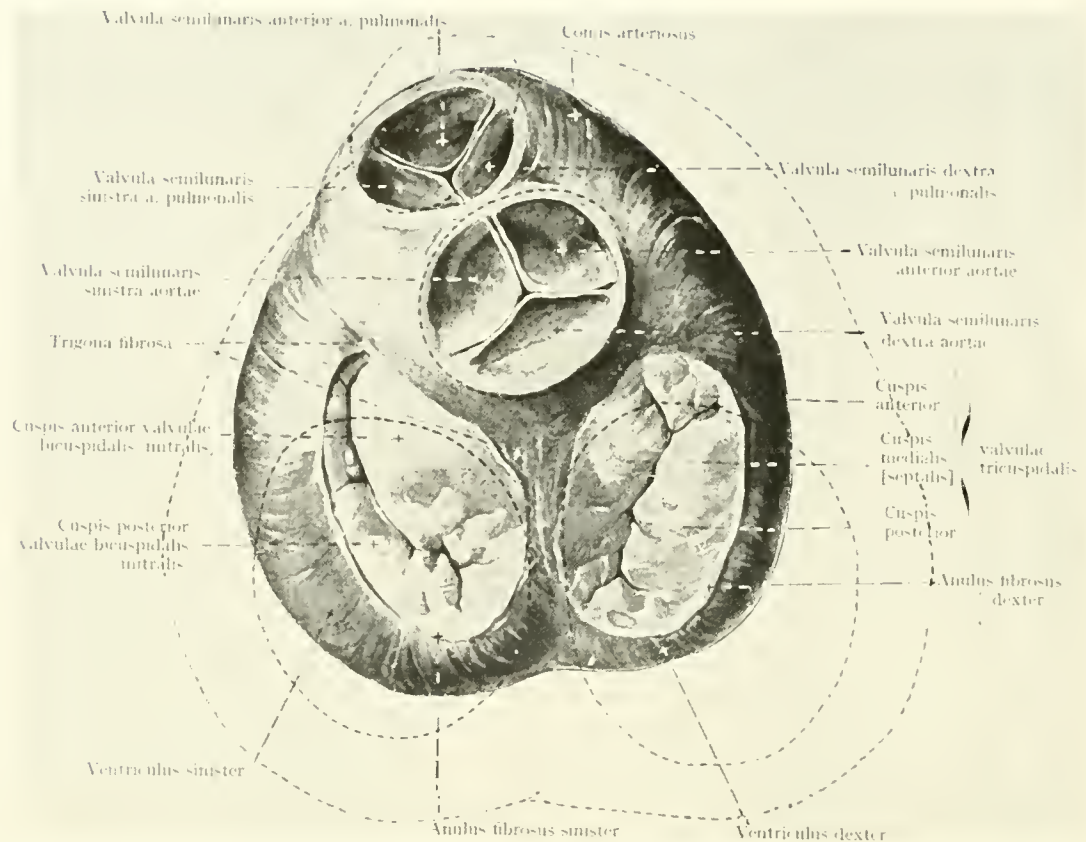


FIG. 4. Base of the human ventricles seen from their cranial aspect after the atria have been removed. The shape of the ostial orifices in the state of contraction differs significantly from the shape in the state of relaxation, as indicated by the dashed lines. [From Spalteholz (148).]

by elastic rebound at the beginning of muscular relaxation.

Many strands of myocardial fibers end with tendinous tissues. Yet one cannot compare them with skeletal muscle, since there is no bone to provide a fixed attachment. In reality, all myocardial fibers end on other myocardial fibers either directly or by insertion of connective tissue. For instance the myocardial fibers of the papillary muscles continue as chordae tendineae, which in turn lead via the bicuspid and tricuspid valve leaflets and the fibrous tissue of the heart skeleton to other myocardial fibers. This arrangement forms a circle of myocardial tissue, although with inclusion of a tendinous segment. Other myocardial fibers, such as many strands in the left ventricular deep bulbospiral bundles, simply form a circle. Since, in the final analysis, all myocardial fibers pull directly or indirectly on other myocardial fibers, the concerted effect of their contraction diminishes each heart cavity more or less concentrically [see also Hawthorne (67)]. It also stands to

reason that all muscle "fiber-rings" which include a noncontractile segment exert during their contraction a pull on the noncontractile segment, storing in it potential energy for release during myocardial relaxation.

The cells of the conduction system have a special position as far as their participation in the contractile process is concerned. They are derived from muscle cells, but their primary function is the fast conduction of excitation. Yet they do contain a small number of myofibrils and therefore must be expected to participate in the over-all myocardial activity. Since nobody has measured their contractile force, it remains a matter of conjecture whether Purkinje cells contribute to any significant extent to the force of ventricular contraction. It may be that their contraction serves only the purpose of diminishing the shear forces which would develop between myocardial and Purkinje cells if the latter remain purely passive. In the longitudinal direction the Purkinje cells are joined to intermediate cells which connect them to myocardial

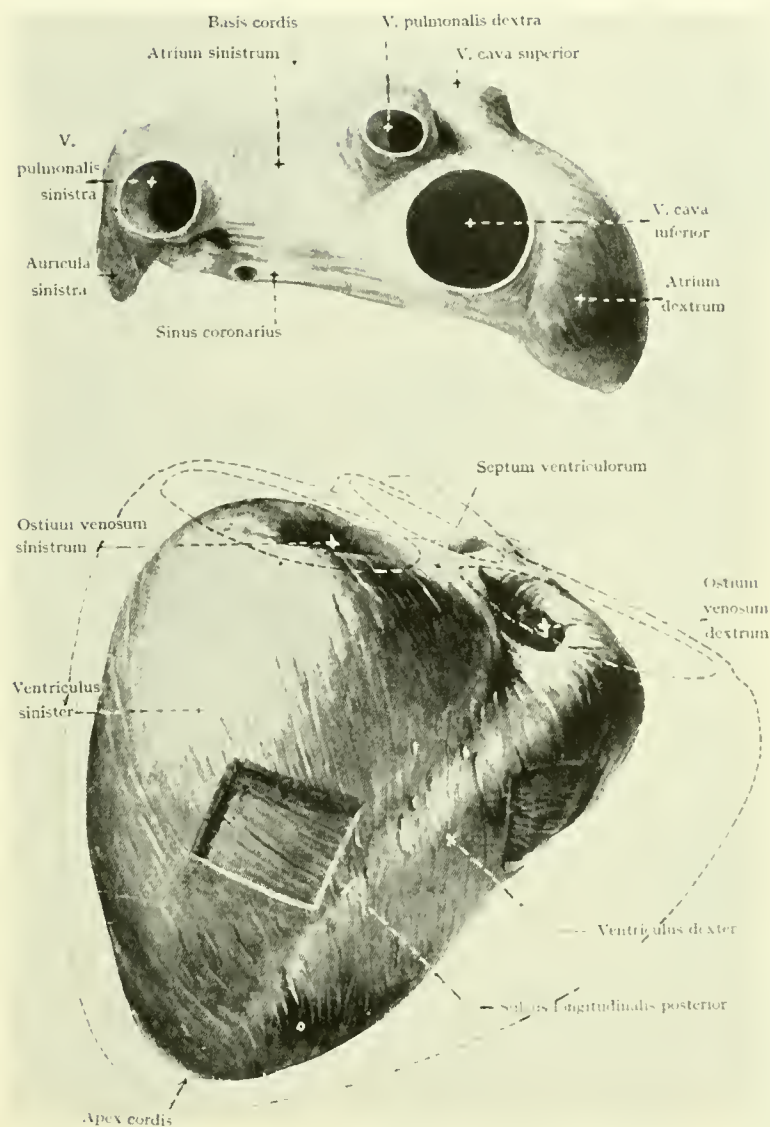


FIG. 5. Superficial muscle layers of the maximally contracted human heart, viewed from the caudal aspect after separation of the atria (above) from the ventricles (below). The ostia of the contracted ventricles can be compared with their state in the relaxed ventricles (dashed lines). The changes in ventricular configuration during relaxation are also indicated by dashed lines. [From Spalteholz (148).]

cells. These intermediate cells contain an increasingly larger number of myofibrils as they approach the true myocardial cells. Merely judging from morphological evidence, they must contribute to some extent to the over-all contractile process.

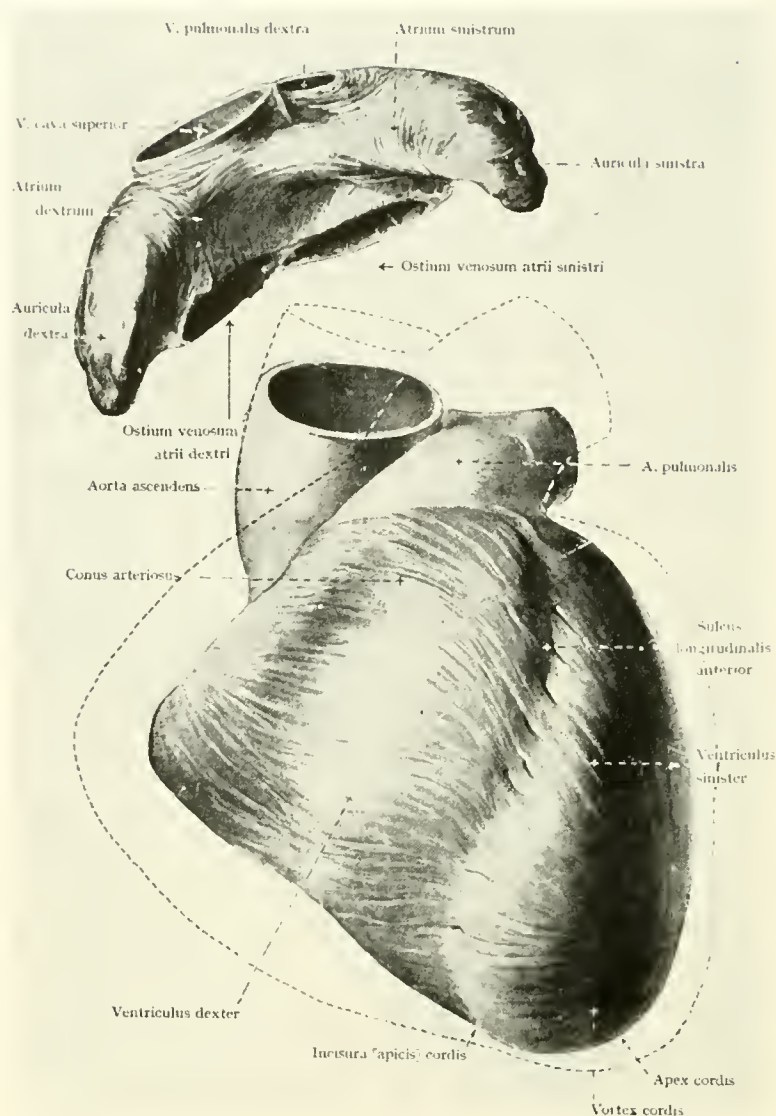
Architecture of the Ventricular Myocardium

Since the ventricles perform more pumping action than the atria, the architecture of the ventricular myocardium has attracted most of the attention of functionally oriented anatomists. Despite extensive description by MacCallum (108), Mall (111), Mönckeberg (114), Benninghoff (10), Robb & Robb (136), Spalteholz (148), and Lev & Simkins

(97), much confusion still prevails. Opinions vary because it is difficult to dissect clearly the complexly arranged, intertwined and crisscrossing discrete muscle bands. Consequently, it is even harder to derive from the anatomic findings a picture of the direction of maximal pull of each muscular component, not to mention the concerted action of several components.

Many of the muscle bands encircle both left and right ventricles. According to the most commonly accepted terminology, one distinguishes four different muscles, the course of which can be best understood from semischematic drawings: the superficial bulbo-spiral (fig. 7), superior sinospiral (fig. 8), deep sinospiral (fig. 9), and deep bulbo-spiral muscle (fig. 10.)

FIG. 6. Superficial muscle layers of the maximally contracted human heart, seen from the ventrocranial aspect after separation of the atria (above) from the ventricles (below). The position changes of the great vessels and the ventricle outlines during relaxation are indicated by dashed lines. [From Spalteholz (148).]



According to Benninghoff (10), who uses a somewhat different classification, there are three interconnected systems which intersect rectangularly: *a*) the outer longitudinal fibers which connect to the outer contour fibers at the ostia; *b*) the ring fibers which encircle the entire chamber and curve around to form fibers of the ventricular septum; *c*) the internal longitudinal fibers which run from the contour fibers toward the apex (figs. 11 and 12). Benninghoff (10) analyzed the function of these various bundles on the basis of careful comparative anatomical studies and in vivo observations. He emphasized the concept that crossing of the fiber layers at right angles results in an over-all reduction of the cavity size, as first postulated by Carl Ludwig. Each of the three systems affects the entire heart and at the same time each of the ventric-

ular cavities. They act in such a manner that a reduction of the heart chambers does not occur equally in all directions but in such a manner and sequence that the cavities are emptied toward their outflow tracts. The evolution proceeded as follows: in lower vertebrates (fish, amphibia) there are no tendinous elements and all muscle bundles are ring shaped. In the mammalian heart secondary valves (atrioventricular) are formed from which the connective tissues of the fibrous rings of the atrioventricular valves and of the chordae tendineae originate and become inserted into the course of the ring-shaped muscle. The fibrous rings become connected to the roots of the arteries and form the solid trigona fibrosa, which furnish new insertions for many myocardial fibers (see fig. 4). In the evolutionary process the

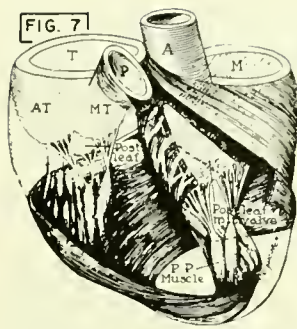


FIG. 7. The superficial bulbospiral muscle as seen from the front of the human heart. *A* = Aorta; *M* = mitral orifice; *P* = pulmonary artery; *T* = tricuspid orifice; *AT* = anterior leaflet of tricuspid valve; *MT* = medial leaflet of tricuspid valve. A V-shaped section is cut from those fibers encircling the left ventricle subendocardially, so that the mitral valve may be seen. A similar band on the right is not sketched in. [From Robb & Robb (136).]

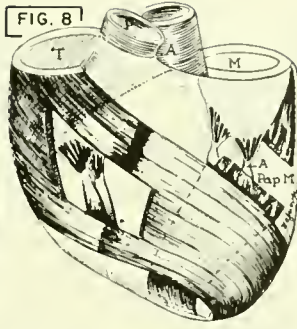
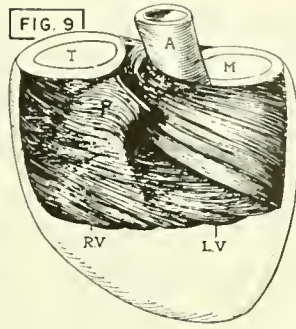


FIG. 8. The superior sinospiral muscle as seen from the anterior surface of the heart. Symbols as in fig. 7. Again the subendocardial layer has been cut through in order to show deeper structures. The window in the right ventricular wall shows the fibers from the trabeculated area running up to the anterior



and medial leaflets of the tricuspid valve. In both of these superficial muscles, blood vessels follow the muscle strands as they encircle the apex. [From Robb & Robb (136).]

FIG. 9. The deep sinospiral muscle as seen from the front. Note the division of the muscle at the posterior inter-ventricular sulcus, with fibers passing anteriorly to form most of the basal two-thirds of the septum; these septal fibers lie just distal to the band of the left head of origin at the base of the aorta. Symbols as in fig. 7. [From Robb & Robb (136).]

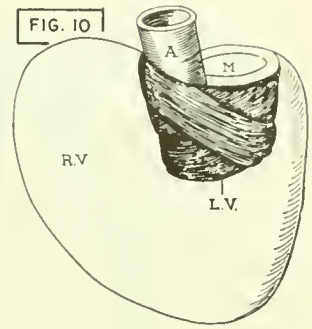


FIG. 10. The deep bulbospiral muscle, a powerful sphincter encircling the left ventricular base and enclosing both the aorta and the mitral orifice within its sweep. [From Robb & Robb (136).]

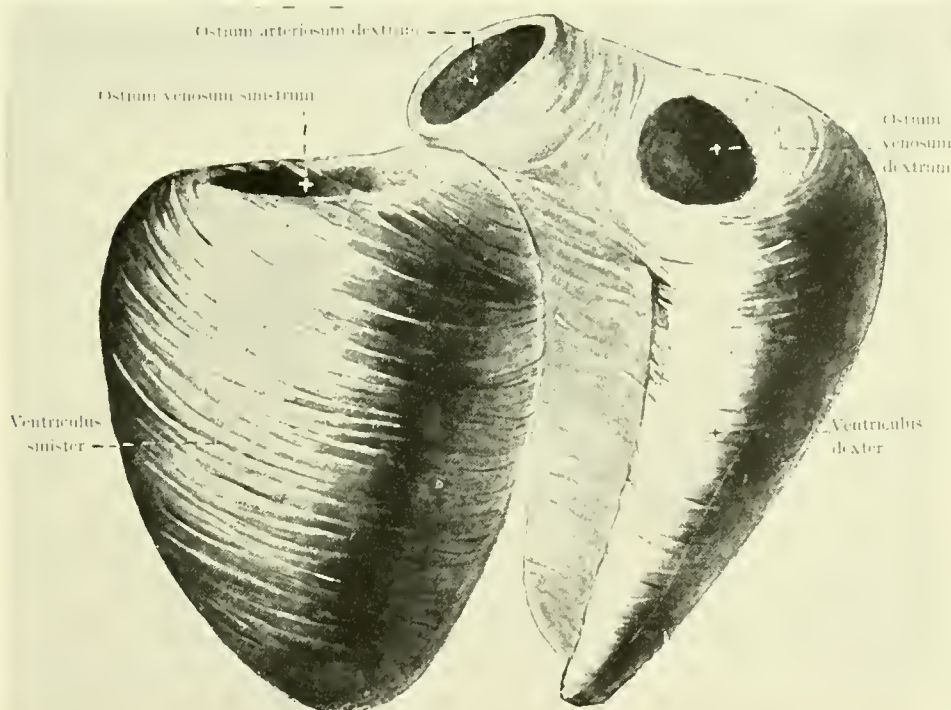


FIG. 11. Human ventricular myocardium after removal of the superficial muscle layers (seen from the caudal aspect). [From Spalteholz (148).]

spongiosa (spongy network of muscle fibers) is gradually reduced by the increasing compacta (solid tissue of muscle fibers). The phylogenetic remainders of the spongiosa are the muscular trabeculae, which are only moderately developed in the mammalian

heart and are almost completely replaced by compacta in the bird heart. In this respect the birds represent the highest functional development. According to Benninghoff (10) the spiral course of the muscle bundles toward the heart skeleton and the

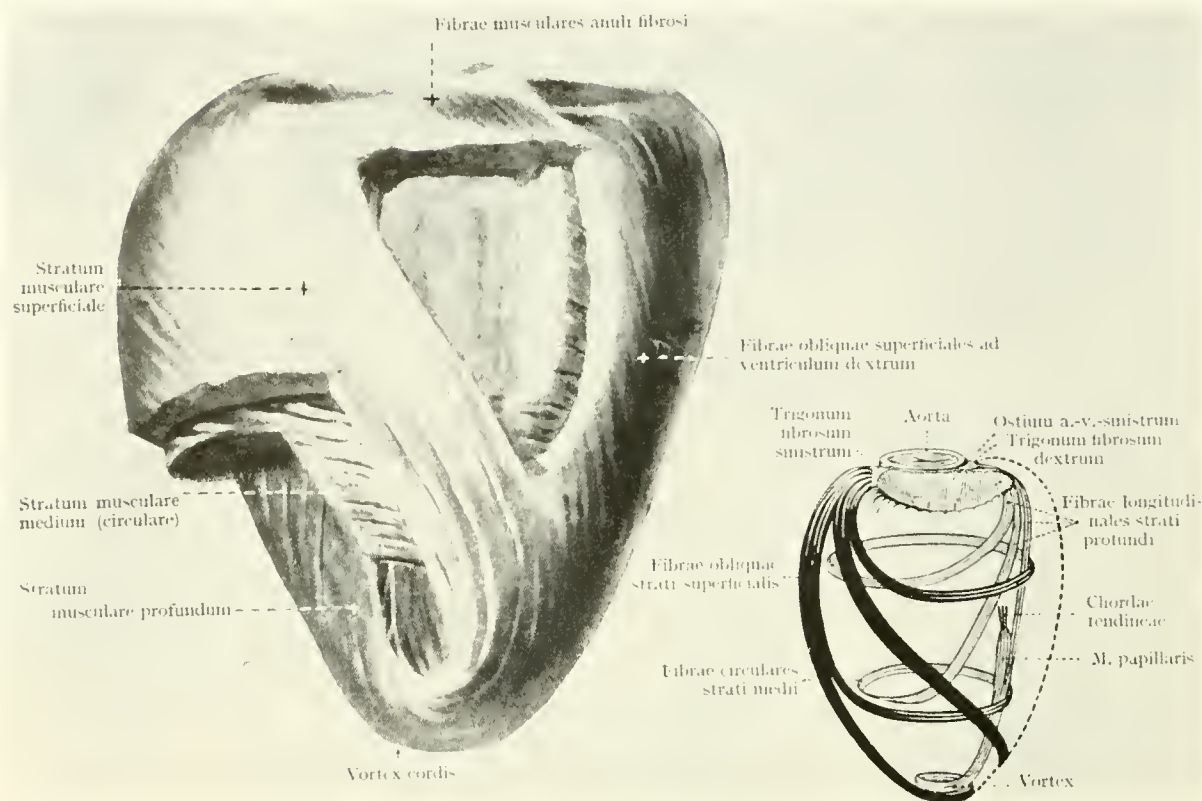


FIG. 12. Course of the left ventricular muscle fibers. *Left*: preparation of human heart after partial removal of the superficial and medial muscle layers (seen from the dorsal aspect). *Right*: schematic presentation of the course of the muscle fibers as viewed from the dorsal aspect. [From Spalteholz (148).]

vortex formation near the apex are more pronounced in the mammalian than in reptile and bird hearts (see fig. 12, right).

Rushmer (139) points out that the division of the heart musculature into "sinospiral" or "bulbospiral" bundles is rather arbitrary and complicates the functional analysis. He suggests the division of the ventricular musculature into two groups of myocardial bundles, the spiral muscles and the deep constrictor muscles (fig. 13). He states in his unsurpassed description, the "functional anatomical analysis points to the direction physiological experimental work should pursue to verify... postulations and to obtain quantitative measurements."

Architecture of the Atrial Myocardium

The atria supply blood to the ventricles through three mechanisms: 1) passively, during the first part of their diastole, by serving as blood collecting chambers as long as the atrioventricular valves are closed by the high ventricular pressure; 2) still

passively, during the second part of their diastole, by serving as channels to permit the passage of blood from the systemic or pulmonary veins into the ventricles once the atrioventricular valves are opened; 3) actively, during atrial systole, by contracting and thereby pushing some blood into the ventricles shortly before the ventricular myocardium begins to contract. Since usually only a small fraction (10–30%) of the blood for ventricular filling is actively propelled by the atrial musculature and the resistance to inflow into the ventricular cavity is negligible, the normal atrial myocardium does not need to be thick walled.

The arrangement of the muscle fibers in the atria is much simpler than that in the ventricles. Two groups of fibers can be distinguished: 1) those which belong to one atrium only, and 2) those which are common to both atria (151).

Group 1: The fibers which lie in the wall of each atrium form muscle rings around the entrance orifices, i.e., the pulmonary veins in the left atrium and the coronary and caval veins in the right atrium. These annular fibers may act as sphincters, possibly

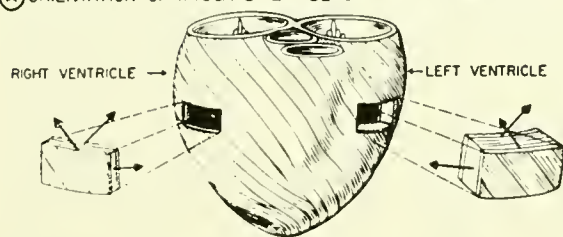
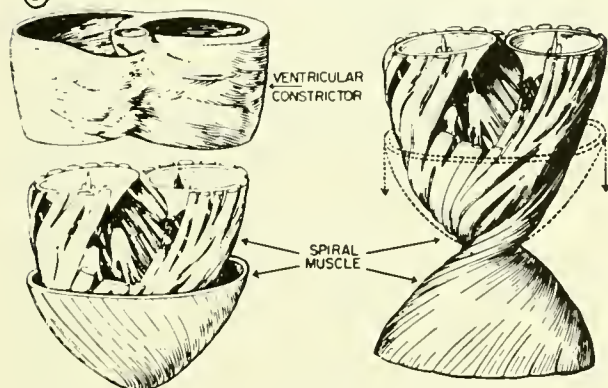
(A) ORIENTATION OF MYOCARDIAL FIBERS IN VENTRICULAR WALLS**(B) FUNCTIONAL COMPONENTS OF VENTRICULAR MUSCULATURE**

FIG. 13. Muscular structures of the ventricles diagrammatically arranged so as to reveal their functional components. *A*: blocks of tissue removed from the walls of the ventricles are composed of three layers of muscle. The myocardial fibers in these layers are oriented roughly in the three general directions indicated by the arrows. *B*: from a functional point of view, the ventricles are formed of two sets of myocardial bundles: *a*, the internal and external layers of spiral muscle, which enclose *b*, the ventricular constrictor muscles. The internal and external investments of the ventricular chambers are composed of the same muscle bundles, which are strongly twisted at the vortex and spiral in opposite directions from the apex toward the base. [From Rushmer (139).]

impeding, though not completely blocking, the backflow of blood into the veins during atrial systole. Looped fibers are also found which run from the anterior to the posterior segments of the atrioventricular junction, directly beneath the endocardium. At many places these fibers bulge into the atrial cavities forming various ridges which are most conspicuous at the inner walls of the atrial appendages, where they are named *musculi pectinati* from their resemblance to a comb.

Group 2: The fibers common to both atria are less numerous and lie superficially with respect to the proper fibers of each individual atrium. They consist of two thin muscle sheets which extend in a transverse direction from one atrium to the other. They can be subdivided into anterior and posterior fascicles. The muscle fibers of the atria and ventricles are separated

by connective tissue except at one place, known as the atrioventricular bundle or bundle of His.

The atrial cavity is surrounded by the thin myocardial fibers of both groups arranged in layers which are partly parallel and partly crisscrossed. The concerted action of all fibers is that, upon their contraction, they diminish the size of the atrial cavity and push blood into the region of least resistance, i.e., primarily into the ventricles, secondarily into the venous orifices. In addition to the main atrial cavity, there is an adjoining cavity formed by the lumen of the atrial appendage, also called "auricle" because of its resemblance to a little ear. The function of the auricles is unknown. Excision of the auricles in various operative procedures does not influence the circulation noticeably. Yet one cannot state bluntly that the atrial appendages have no function at all, since in a complex system, such as the heart, the function of a missing part may often be taken over or substituted by increased activity of other components. The mere presence of the atrial appendages results in an increase in the cardiac reserve. According to Benninghoff (10) and Böhme (14), the atrial appendages fill the space which is created within the pericardial sac during ventricular systole, as the ventricles eject blood into the large arteries and decrease in size. During this period the atrial appendages accommodate a considerable amount of blood. This blood is immediately available at the beginning of the rapid ventricular filling phase to be transferred into the ventricular cavities.

PRESSURE AND FLOW EVENTS DURING THE CARDIAC CYCLE

Historically the cardiac cycle was first divided into "systole," or period of contraction, and "diastole," or period of relaxation of the ventricles. It was soon recognized that the terms systole and diastole should refer equally to the atrial contraction and relaxation, although the ventricular events were most conspicuous in the gross observation of cardiac activity. Since the atrial contraction precedes that of the ventricle, terminological difficulties arose as to which systole was meant in describing the time sequence of cardiac events. As knowledge about the heart's action increased, it was also deemed necessary to subdivide the cardiac cycle in greater detail [see also Mackenzie (110)]. With the advent of methods for precise pressure recording from the cardiac chambers and great vessels, the ventricular pressure tracings

became the deciding guidelines for characterizing the phases of the cycle. The generally adopted subdivisions of Wiggers (156) stem from this era. Since other landmarks of cardiac activity such as flow, volume changes, or biochemical processes were difficult to record adequately, they were only correlated with the pressure curves at a later date.

It is still impossible to subdivide the cardiac cycle according to the most important physiological events: the blood flow into and out of the cavities. The approximate beginning and end of systolic ejection can be determined from simultaneous pressure tracings in a ventricle and in an arterial outflow tract. However, the precise timing of flow is only possible through direct recording of flow either at the root of the aorta or at the pulmonary artery [see also Moscovitz & Wilder (117)]. The recent advent of refined flowmeters will probably necessitate some adjustments in the original Wiggers scheme of the cardiac cycle. For the time being it is still preferable to retain the well-established scheme and to fit modifications into it, rather than to advocate a completely new one [see also Horowitz (80)].

Figure 14 [modified from Wiggers (156, 159)] illustrates in schematic form the sequence of pressure events during the cardiac cycle in the left ventricle, left atrium and aorta, and the volume changes in the combined ventricles [from Henderson (69)]. For time correlation, tracings of the heart sounds and of the electrocardiogram are added. This composite chart is mainly based on curves obtained in animal experiments.

The cycle is divided into two periods, systole and diastole. The former begins with the rise of ventricular pressure caused by ventricular contraction (fig. 14, 1) and ends at the onset of myocardial relaxation, 4, at the point when ejection actually ceases. This point then also represents the beginning of the diastole. The systolic period is subdivided into 1–2, isovolumetric ventricular contraction (50 msec); 2–3, maximum ventricular ejection (90 msec); and 3–4, reduced ventricular ejection (130 msec). The diastolic period is subdivided into 4–5, isovolumetric ventricular relaxation (120 msec), which includes a phase occurring just prior to the incisura and formerly called protodiastole (40 msec), plus the phase formerly known as isometric relaxation (80 msec); 5–6, rapid ventricular filling (110 msec); 6–7, slow ventricular filling or diastasis (190 msec); and 7–1, ventricular filling by atrial contraction (60 msec).

Numerous other cyclical events occur with each

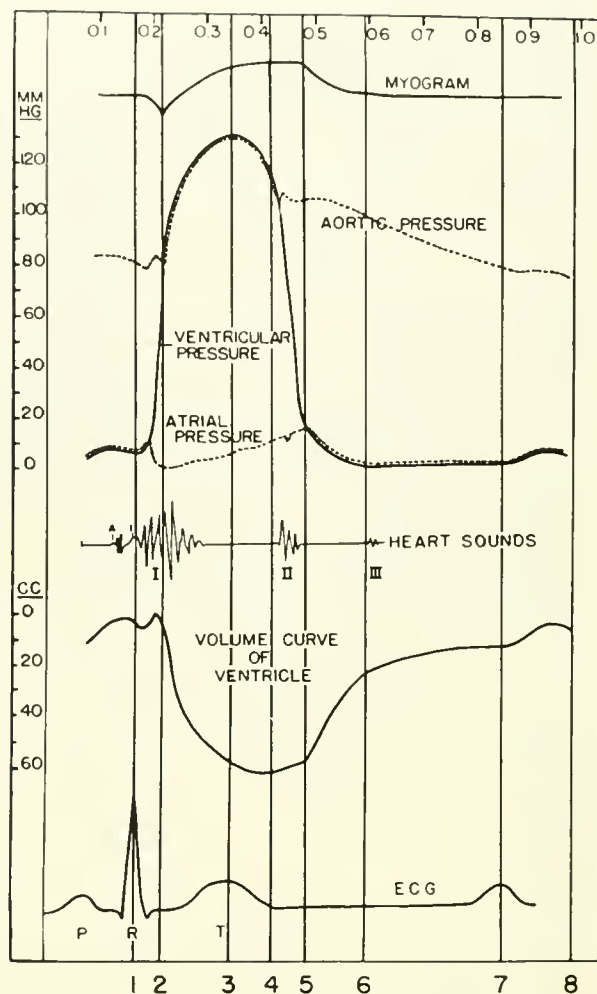


FIG. 14. Scheme of the cardiac cycle. Time, totaling 1 sec, on upper margin. Numbers under lower margin indicate beginning and end of phases. Period of ventricular systole lasts from 1 to 4, period of ventricular diastole lasts from 4 to 1. Detailed description in text. [Figure (but not numbers in text) slightly modified from Wiggers (159).]

heart beat. They are correlated timewise with the phases of the pressure-volume cycle as follows.

1–2: *Isovolumetric ventricular contraction*. During this phase the myocardium builds up tension and this gives a fast rise of intraventricular pressure without change in the volume of blood contained in the ventricular cavity. The intraventricular pressure must rise to the level of the diastolic pressure prevailing in the aorta (or pulmonary artery) before blood can be ejected from the ventricles during the next two phases. The term “isovolumetric contraction” suggested by Rushmer (139) should supersede the older term “isometric contraction,” since at the beginning of this phase there is an actual shortening

of the fibers of the papillary muscles and trabeculae carneae which results in a tension of the chordae tendineae, and an approximation of the atrioventricular valves (139). Simultaneously, there is a passive stretching of the other still relaxed myocardial layers, mainly those of the outer walls of the heart [see also Hawthorne (67), Anzola (4), and Burton (29)]. The older term "isometric contraction" had the misleading implication that all myocardial fibers contract simultaneously and isometrically from the very start. Since in fact some muscle fibers shorten whereas others are passively lengthened during this phase, while the intraventricular volume remains constant, the term isovolumetric contraction provides a more accurate description than isometric contraction. Apparently instrumentation has not yet been refined sufficiently to decide whether or not there is in this phase a brief "latent relaxation" of cardiac muscle fibers as there exists in skeletal muscle fibers.

The shortening of the ventricle in the longitudinal axis results in a descent of the atrioventricular junction which in turn expands the atrial cavities. This leads to a precipitous lowering of the atrial pressure (fig. 14) which is often observed even before the ventricle ejects blood. The ventricular muscle fibers contract in a successive order, probably following the same time sequence as their depolarization (75, 142). As a consequence the blood contained in the ventricular cavity is pushed from the apex region toward the center of the ventricle and moves thereby closer to the outflow tract. The subsequent ejection from the ventricles can be looked upon as a continuation of the intraventricular movement of blood which already starts before the semilunar valves open. At the same time the ventricular cavity changes from a cylindrical to a more spherical shape, which from the energy standpoint represents a more economical way of discharging the ventricular content, once the aortic diastolic pressure is overcome. As pointed out by Rushmer (139), the asynchronous contraction of the ventricular myocardium readily explains the brief upward deflection at the beginning of isovolumetric contraction in the ventricular volume curve described by Wiggers (156) in fig. 14. This was formerly interpreted as an artifact in the recording.

Some arbitrariness is involved in determining accurately the start of isovolumetric contraction. In all pressure tracings the upward movement begins slowly in the form of a rounded curve. There is no abrupt beginning, inflection, or break. This becomes especially evident if one records the pressure events

by drawing out the time axis with fast moving paper as can be easily done today with electrical recording apparatus. The rounded beginning of the upward limb results from the combined effect of *a*) the contraction of the papillary muscles, and *b*) the simultaneous passive distention of some of the muscle fibers in the ventricular wall. Whenever the transfiguration of the ventricle causes a detectable rise of intraventricular pressure, then by convention the ventricular isometric contraction is said to begin. The fact that the different strands of myocardial fibers contract in sequence rather than simultaneously may also explain the great variability of the slopes of the pressure tracings in the early part of isovolumetric contraction.

The steepness of the slope during isovolumetric contraction is predominantly determined by the forcefulness of the fiber contraction. If the difference between the end-diastolic ventricular and end-diastolic aortic pressure remains unchanged, the duration of the ventricular isovolumetric contraction is shortened by sympathetic or sympathomimetic stimulation and lengthened by agents or conditions which depress the sympathetic control of the heart [Cotton & Maling (35), Gleason & Braunwald (54); see also Reeves *et al.* (133)]. Thus in forcefully contracting ventricles, the slope will be steeper than in feebly contracting preparations.

The atrioventricular valves close approximately at the beginning of isovolumetric contraction; the opening of the semilunar valves marks the end of this phase. The precise moment of the valve actuation is difficult to establish experimentally (discussed in the section on heart valves). In the interval between closure of the atrioventricular valves and opening of the aortic and pulmonary valves, the blood contained in the ventricular cavities is temporarily isolated from the fluid columns in the atria and arteries. However, the ventricular content does not remain still (10). In fact the blood which rushed into the ventricles at high velocity during diastole may aid in expanding the ventricular cavities. Since the inflow is primarily directed toward the apex, it is this part of ventricular wall which could be preferentially expanded. As the papillary muscles and trabeculae carneae begin to contract, the movement of the blood is deviated toward the outflow tract. This change in direction of flow is favored anatomically by the fact that the axis of the inflow tract and that of the outflow tract form an angle. In other words, the inflowing blood probably does not come to a complete standstill in order to reverse its direction of flow for ejection into the

arteries, but rather it keeps flowing in a curve from the main direction of the inflow tract toward the outflow tract. This translocation of blood within the ventricle during the isovolumetric phase is energy preserving. In fact, there seems to be rather little turbulence and not always complete mixing of blood during this "intraventricular" streaming from the inflow side to the outflow region. This explains why the streamlining of flow in the venous circulation is not always completely interrupted by the passage of blood through the ventricle. For example, the systemic venous blood is transferred into the pulmonary arteries in such manner that superior caval blood reaches predominantly the right lung and inferior caval blood the left lung [see also Bucher *et al.* (27)]. Obviously, the possibility of incomplete mixing deserves attention when samples of so-called mixed venous blood are drawn.

How much does the velocity of the blood flow decrease during the transit in the ventricle? In the resting organism with a slow heart rate, the velocity of blood streaming into the ventricle toward the end of diastole is rather small, as may be surmised from the fairly flat portion of the ventricular volume curve. When the cardiac output is elevated, the velocity of the intraventricular flow during isovolumetric contraction will probably increase for two reasons: 1) the velocity of end diastolic ventricular inflow increases through a shortening of diastole due to high heart rates and through a more forceful atrial contraction; 2) the transit time through the ventricle is shortened by the more powerful and often shorter myocardial contraction. Such higher intraventricular flow velocities under sympathetic activity could then result in a better energy conservation by not letting the speed of blood flow slow down too much before ventricular ejection begins again.

[It is the feeling of the editors that there is not sufficient evidence to show that continued translocation of blood within the ventricular cavity during isovolumetric contraction could contribute significantly to the subsequent ejection. Ed.]

2-4: *Rapid and reduced ventricular ejection.* As soon as the pressure in the ventricular cavities exceeds that in the aorta or the pulmonary artery, the blood is suddenly ejected. Although flow is created by a difference between the intraventricular and arterial pressures, an inspection of pressure curves alone, simultaneously recorded from the ventricle and the root of the artery, furnishes only meager information about the rate of volume flow and its time course. However, from simultaneously recorded flow and

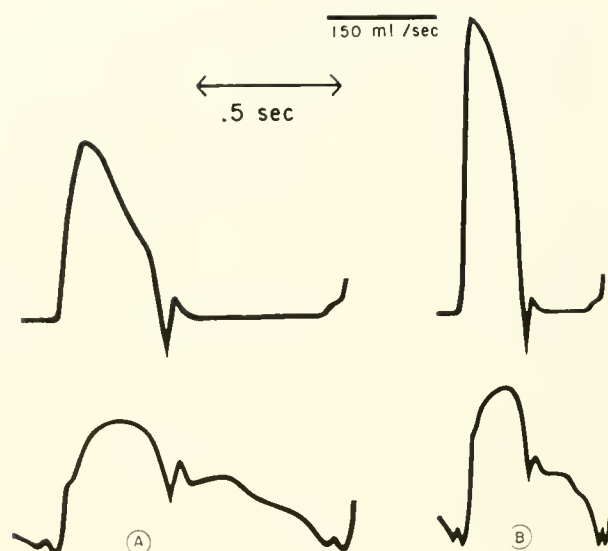


FIG. 15. Phase relationships between pressure and flow as revealed by simultaneously recorded curves from the ascending aorta of a conscious dog. *Upper tracings:* rate of volume flow measured with a permanently implanted electromagnetic flowmeter. *Lower tracings:* aortic pressures obtained through a permanently implanted cannula leading to a strain gauge manometer. *A:* curves from the quiet reclining animal. *B:* curves from the animal running behind a car during moderate exercise. [Original curves by the courtesy of Frederick Olmstead, Cleveland Clinic, Cleveland, Ohio (personal communication, 1961).]

pressure curves in the aorta or in the pulmonary artery, the process of ventricular ejection is now fairly well understood [Wetterer (155)]. The ejection starts abruptly (fig. 15). The blood column in the root of the aorta, which is practically stationary at the end of diastole and during isovolumetric contraction, is rapidly accelerated and pushed toward the periphery. The greatest flow acceleration occurs during the steeply ascending limb of the aortic pressure curve, so that the highest flow rate (peak of the flow curve) is actually reached prior to the summit of the pressure curve. When the flow then becomes less rapid, the phase of reduced ejection is said to begin. The border between rapid and reduced ejection is quite arbitrary. When only pressure and cardiometer curves were available [Wiggers (156)], it was difficult to determine from the gradual leveling off of the downward limb of the volume curve when the rapid ejection started to slow down. The summit of the ventricular pressure curve was thought to indicate the end of rapid ejection (fig. 14). It is now known that the flow slows down earlier, since the peak of the flow curve definitely precedes the peak of the ventricular or aortic pressure curve (upper tracings

in fig. 15). The fact that the ventricular and aortic pressures continue to rise even after the flow rate starts to drop is not surprising, since during the period of reduced ejection, blood continues to accumulate in the aortic arch. Because aortic pressure at any one instant is determined both by the distention of the arterial walls with blood coming from the ventricle and by the runoff into the periphery, the pressure continues to rise as long as more blood enters the aortic arch than runs off toward the periphery. There is no fixed and easily definable time relation between the summits of the flow and pressure curves, because the factors determining the position of each of the summits are numerous and variable (149).

Some aspects of the time relation between the flow and pressure curves *A* and *B* are illustrated in figure 15. During exercise the rapid ejection occupies a relatively shorter portion of the total ventricular ejection. In this example the whole ventricular ejection lasts 374 msec at rest and only 234 msec during exercise. However, the delay between the summits of the flow and pressure curves is 109 msec, in both cases, or 29 per cent of the whole ventricular ejection at rest, and 46 per cent during exercise. In other words, during exercise the aortic pressure continues to rise relatively longer after the aortic flow rate has started to drop, indicating that there is relatively more blood accommodated in the central arteries (arterial compression chamber) during systole. This also means that, when ventricular ejection ceases, there is a higher aortic pressure and consequently a larger amount of peripheral runoff during early diastole. Such conditions help to maintain greater tissue perfusion in the active organism.

The configuration of the aortic flow curve is not the same in the organism at rest and during exercise or sympathetic stimulation. At rest, the descending limb of the flow curve first declines gently, then progressively faster, forming thereby a shallow hump (see fig. 15*A*). During exercise the ascending limb is steeper and the descending limb declines precipitously (fig. 15*B*). This pattern indicates: 1) an increase in the myocardial contractile force, which continues to exert its strong effect after the end of the isovolumetric contraction phase and achieves a more rapid flow acceleration; 2) a longer duration of flow at near maximal velocity (Olmstead, personal communication); and 3) a faster return to the beginning of myocardial relaxation. Despite shortening of the ejection phase, the stroke volume, which can be calculated from the area under the curve, is approximately the same during moderate exercise as it is at

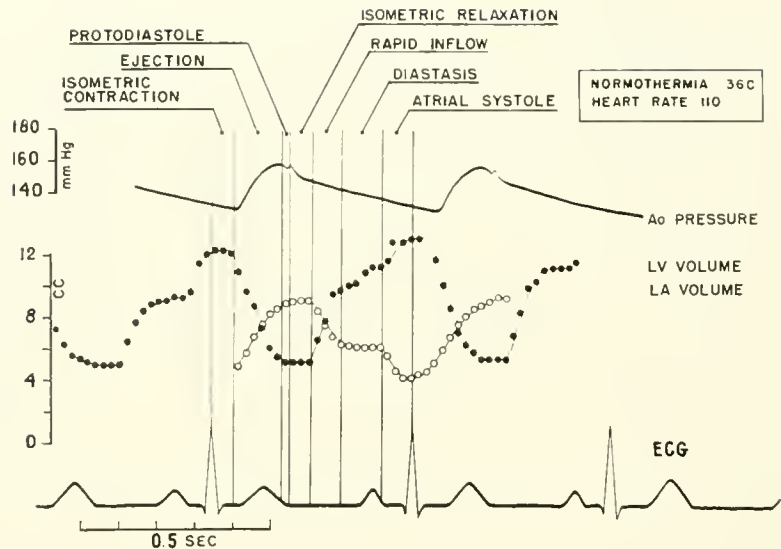
rest. However, during strenuous exercise (running of dog at 16 miles per hour over rough terrain) the stroke volume appears to be increased by approximately 25 to 40 per cent (Olmstead, personal communication). Whether or not there is always an increase in stroke volume during exercise is still a matter of debate among various investigators [see also Rushmer (139)].

Toward the end of the reduced ejection phase the intraventricular and aortic pressures drop quickly. The ejection stops and forward flow in the ascending aorta ceases shortly after closure of the semilunar valves as seen by the crossing of the flow curve through the horizontal zero flow line in figure 15. Flow in the root of the aorta near the valves momentarily reverses its direction, because of a translocation of blood into the sinuses of Valsalva and the coronary vessels, which helps to close the aortic valves. Although there is a brief backflow near the valves, in the more distal part of the aorta the flow continues forward for a while, since the energy momentarily stored in the distended aortic arch propels the blood to the area of lower pressure, i.e., the peripheral vessels (compression chamber effect). The precise moment of valve closure cannot be easily correlated with the pressure and flow curves. It can be stated from the flow curve that the valves must have closed at least by the time when the downward deflection is suddenly stopped (fig. 15) and after which blood again is propelled forward in the ascending aorta. How much blood is regurgitated into the ventricles and how much flows into the coronary arteries while the valves are in the process of closing, has not yet been determined.

4-5: *Isovolumetric relaxation.* It is also difficult to establish the exact moment when the myocardial fibers start to relax after maximal shortening. Wiggers (156) took the steepening of the decline in the ventricular pressure curve prior to the deepest point of the aortic incisura as the beginning of the relaxation process and referred to the brief interval from the beginning of muscular relaxation to semilunar valve closure as the protodiastolic phase. Since little is gained by singling out this interval, which cannot be accurately measured, the phases of protodiastole and isovolumetric relaxation will be treated here as a single process as Wiggers (159) also suggested in his recent discussion on this subject.

It appears reasonable to assume that, just as the contraction began asynchronously, some myocardial fibers will begin to relax earlier than others. However, no direct measurements are available to document this hypothesis. At the end of isovolumetric relaxation,

FIG. 16. Phase relationships between aortic pressures, Ao ; left ventricular volume, LV , (dots); atrial volume, LA , (open circles); and electrocardiogram, ECG , in an anesthetized normal dog with a spontaneous heart rate of 110/min. The pressure tracings were simultaneously recorded and correlated with the volume measurement from the kinematographic frames. [Original curves and labeling by courtesy of Peo Gribbe, Wenner-Gren Research Laboratory, Norrtull's Hospital, Stockholm, Sweden (personal communication, 1961).]



the intraventricular pressure drops to the level of the atrial pressure. The pressure decline, like the pressure rise, is more rapid under the action of epinephrine (158, 124) and apparently also in exercise. Therefore, with epinephrine and during exercise the duration of the isovolumetric relaxation phase is shorter for the same pressure difference between the incisura and atrial pressure. Neither the precise moment of the valve opening at the end of isovolumetric relaxation nor the pressure difference necessary to actuate them has been satisfactorily determined as yet. One usually takes the decline in atrial pressure after the V point as an indication that the atrioventricular valves have just opened and flow through the orifice has begun. The crossing over of the atrial and ventricular pressure tracings is therefore taken as the end of isovolumetric relaxation. However, even with the most careful recording, it is difficult to establish such a crossing over without artifacts. Since at this part of the cardiac cycle the heart has become a low-pressure system, instrumentation errors are commonly experienced with positioning of pickup devices, movement artifacts, lack of sensitivity, Bernoulli effect, and lack of a common and reliable reference zero pressure level.

5-7: *Rapid and slow ventricular filling.* There is no satisfactory procedure to measure directly the inflow of blood from the atrium into the ventricle. The best information stems from X-ray kinematographic studies such as those of Rushmer (139), Chapman *et al.* (31, 32), Gribbe *et al.* (56). A good time resolution was obtained by Gribbe, who took 40 to 50 frames per sec using an image intensifier. The individual frames of film were projected and the volume was

calculated from the contrast silhouette of the left atrium and ventricle, assuming that the left ventricular cavity resembles an ellipsoid of rotation. Figure 16 illustrates the steep upward slant of the curve during the phase of rapid ventricular filling. The incline of this part of the curve is even steeper than the decline of the curve during rapid ventricular ejection, indicating that blood actually rushes into the ventricle faster than it is ejected from the ventricle. This observation has an important bearing upon the concepts of the forces which bring about ventricular filling (see later section). After the rate of ventricular inflow has reached its maximum, it begins gradually to slow down until finally the curve tends to level off. There is no distinct break which could serve as a criterion for precise determination of the end of the rapid filling phase and the beginning of the slow phase. Nevertheless, the distinction between these two phases remains useful at slow heart rates, as for instance under strong vagotonic influence, because the slow phase of ventricular filling then lasts much longer than depicted in figure 16.

7-1: *Filling by atrial contraction.* With the contraction of the atrial myocardium an additional volume of blood is pushed into the ventricle, as shown by the sudden final incline of the curve in figure 16. The contribution of atrial contraction to ventricular filling has been much debated [see Mitchell *et al.* (113)]. According to the measurements of Gribbe *et al.* (56), it should amount to about 20 to 25 per cent of the volume entering the ventricle. Atrial pressure drops after the peak of atrial systole but seemingly without a measurable decrease in ventricular volume by backflow through the atrioventricular valves. If

ventricular pressures are recorded with instruments of sufficient sensitivity, the transfer of the atrial pressure rise can be observed on the ventricular pressure tracing, since atrium and ventricle form a common cavity during atrial systole. Similarly, after the peak pressure of atrial systole has been reached, the pressure drops not only in the atrium but also in the ventricular cavity. When the atrioventricular valves actually close is still a matter of debate (see also later section). It may well be that the large valve leaflets begin to approximate each other at the moment when the atrial pressure starts dropping and that they continue to move toward each other because ventricular blood flows into the large spaces behind the closing leaflets. Therefore, the valves may start to close at a time when the ventricular pressure is decreasing slightly. Complete closure would then be achieved when the dropping atrial and intraventricular pressures level off (Z point in atrial pressure curve).

As the heart rate becomes faster under sympathetic stimulation or in exercise, the period of slow ventricular filling is progressively shortened by an earlier onset of the atrial systole [see Mitchell *et al.* (113)]. At heart rates above 120 per min the phase of slow ventricular filling is more or less abrogated (56). Figure 17 illustrates how at a heart rate of 160 per min the phase of rapid ventricular filling is directly followed by the inflow due to atrial contraction. In these curves one cannot discern the usual hump in the upstroke of the filling curve which occurs when rapid ventricular filling changes to slow ventricular filling before the atrium adds its contribution. It is likely that at still faster heart rates, the atrial component of the curve blends completely with the inclined tracing characteristic of rapid ventricular filling. At extreme degrees of tachycardia even the phase of rapid ventricular filling may be encroached upon. This would explain why the stroke volume decreases at very rapid heart rates since there is not sufficient time for adequate filling of the ventricle.

The force of atrial contraction usually varies concomitantly with that of ventricular contraction. Therefore, the percentile contribution of atrial systole to ventricular filling is lower under vagal influence and higher under sympathetic excitation. In extreme tachycardia, when atrial systole begins during the phase of rapid ventricular filling, the actual contribution of the atrium to the filling of the ventricle may be as high as 30 to 40 per cent. The atrial contraction would then serve to increase the pressure difference between the atrium and ventricle in the later part of the rapid filling phase and thereby

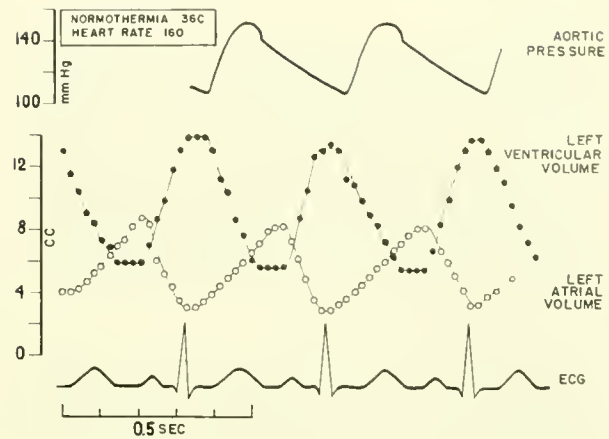


FIG. 17. Phase relationships among aortic pressure, left ventricular volume (dots), atrial volume (open circles), and electrocardiogram (ECG), in an anesthetized normal dog with a spontaneous heart rate of 160/min. The pressure tracings were simultaneously recorded and correlated with the volume measurement from the kinematographic frames. [Original curves and labeling by courtesy of Peo Gribbe, Wenner-Gren Research Laboratory, Norrtull's Hospital, Stockholm, Sweden (personal communication, 1961).]

produce a maximal velocity of inflow throughout the entire, though brief, phase of rapid ventricular filling.

CORRELATION OF OTHER CARDIAC EVENTS WITH THE CARDIAC CYCLE

The time sequence of cardiac events originally described by Wiggers (156) was based upon those pressure changes in the circulatory system which were measurable at the time. However, during the last three decades our trend of thinking about cardiac events has been greatly affected by the progress of electrocardiography. At the very beginning of the investigations of the field (about 1910-1920) the electrocardiogram could only be correlated secondarily with the time course of the more easily measurable pressure events (138). Nowadays one can record electrocardiograms with a higher degree of time resolution than intracardiac pressures. For this reason it is rather common to use the electrocardiogram as the basis or guideline for dividing the cardiac cycle into phases and then to fit secondarily the pressure and flow events into the patterns of the electrical events (17, 157). However, there is a varying time lag between electrical and mechanical events under different experimental conditions [see Luisada & Liu (104)], so that such a correlation system is not entirely satisfactory.

Atrial Pressures

The recording of atrial pressures is beset with considerable experimental difficulty, as is the case with all fast changing phasic events in low pressure systems. The finer details of atrial pressure contours are therefore often affected by artifacts from impacts or vibrations which make it difficult to arrive at accurate deductions concerning atrial flow dynamics. Indeed the atrial pressure pulse contour depicted in figure 14 is highly schematized.

Atrial pressure begins to rise at the onset of atrial systole (A wave). Since at this moment the atrium and ventricle form a common cavity, the height which the atrial pressure attains is influenced by the volume distensibility characteristics both of the atrium and of the ventricle, in addition to the rate of translocation of the fluid from one part of the cavity into the other. The resistance to flow through the normal atrioventricular orifice is so low that it cannot be measured with presently available techniques.

Little is known about the synchronicity or asynchronicity of the contraction of atrial muscle fibers. The excitation wave spreading over the atrial walls proceeds from the sino-atrial node. Therefore it can be assumed that the contraction, which follows depolarization after a brief interval, similarly proceeds in a wave. The concept of asynchronous atrial muscle contraction is based on the premise that the delay between depolarization and contraction is the same for all atrial muscle fibers. It is not certain that this is the case. A contractile wave is difficult to demonstrate conclusively and consistently by means of slow motion pictures.

The drop in atrial pressure, after the pressure has reached a peak during atrial contraction, is probably caused by the beginning of atrial muscle fiber relaxation. Again, it is not possible to state whether this occurs synchronously or in a sequential order and to state what effect this process has on the flow dynamics. From the configuration of the atrial pressure curve one cannot necessarily infer the exact onset of atrial muscle relaxation. Just as the ventricular pressure curve can still rise although the rate of ejection already declines (see fig. 15), the atrial pressure could well start to decrease before or after the relaxation in the atrial musculature actually begins. The convention of calling the leveling off of the declining atrial pressure curve the "end of atrial systole" is also arbitrary [Opdyke *et al.* (126); Opdyke & Brecher (125)].

There is often a brief period (Z point) during which the atrial pressure curve remains level after its decline

from the systolic rise. This is the last moment at which the atrial and ventricular cavities are probably still in communication before complete closure of the atrioventricular valves. The atrial Z point pressure is almost equal to the ventricular end-diastolic pressure because the rate of ventricular inflow has become minimal at this moment. Therefore it is fairly safe to take the Z point as a representative of end-diastolic ventricular pressure. It is definitely more accurate to use the Z point than the mean atrial pressure, which depends upon numerous factors unrelated to the end-diastolic ventricular pressure, such as integration of artifacts and peaks at the A, C, V points (126).

After the Z point the atrial pressure often rises briefly and precipitously (C wave). This pressure rise, frequently accompanied by vibrations, is ascribed to the bulging of the atrioventricular valves into the atrial cavity during ventricular isovolumetric contraction. Immediately following the sharply peaked C wave, atrial pressure usually declines to a level corresponding to atmospheric zero in an open-chest preparation (see fig. 14), or to near-zero transmural pressure in a closed-chest organism. It is believed that this pressure drop is caused by the pull of the papillary muscles on the atrioventricular valve leaflets and by the descent of the atrioventricular junction which suddenly enlarges the atrial cavity. The bottom of the pressure drop is called the X point (or wave). Thereafter atrial pressure rises slowly up to the V point (or wave) located at the end of ventricular isovolumetric relaxation. The pressure rise from the X point to the V point is probably caused by an inflow of blood which distends the atrial walls. The atrial pressure drop (Y point or wave) after the opening of the atrioventricular valves results from the rapid transfer of blood into the ventricular cavity in which a lower pressure prevails. While it is assumed that the actual opening of the atrioventricular valves occurs at the summit of the V wave, there is some debate whether or not it occurs slightly afterward [see also Nixon (120)].

A minor change in the conventional labeling of atrial pressure tracings has been used by Kaplan (88). Without mentioning the Z point, he refers to the small decline in pressure which frequently follows atrial systole, before the C wave, as the X wave. Then he designates the pressure decline after the C wave as the X¹ wave. There is no conspicuous advantage to this system of notation.

Electrocardiogram

Since the electrocardiogram is easily obtainable and serves as an important diagnostic tool, considerable efforts have been made by theoretical and clinical scientists to correlate timewise electrical and mechanical events of cardiac contraction. Nearly half the large volume of the *Physiology of the Heart*, by Schütz (144), is devoted to this subject and should be referred to for detailed information.

From the standpoint of cardiac pumping, the electrocardiogram is principally of interest insofar as it may furnish a convenient method of determining precisely the course of mechanical events without resorting to surgical interventions, cannulations, etc. Present attempts along these lines are still inadequate. They are also theoretically limited for the following reasons: *a)* although the electrical event always precedes the mechanical event, it is not known whether the time intervals between depolarization and beginning of contraction are identical in all heart muscle fibers. *b)* There may be differences in the rates of impulse propagation along various fibers resulting in varying rates of contraction once depolarization has started at one point. *c)* As repeatedly emphasized by Rushmer (139) and Scher (142), there is considerable mechanical asynchronicity in the contraction of cardiac muscle fibers, which cannot be completely unraveled by recording the over-all electrical changes from a large mass of tissues such as the heart. *d)* There are possibly time differences between the right and left heart depolarizations and contractions, but these differences are inconstant and change with various factors.

An example of the difficulties encountered in attempting to establish empirical time correlations in the cardiac cycle is shown in figure 18. Using normal anesthetized dogs, Gribbe *et al.* (57) studied the volume changes in the cardiac chambers with cineradiography and timed the events with the conventional electrocardiogram. Comparison of the time relations in figure 19 with those shown in figures 14 and 18 reveals considerable discrepancies.

Vibrocardiogram (Apex Cardiogram)

The intracardiac pressures are not easier to correlate with the electrocardiogram than with a number of other mechanical events [e.g., Harrison *et al.* (65)]. For instance, the classical mechanocardiogram or apex cardiogram, now often referred to as precordial vibrocardiogram, offers a good example of the present limitations in the description of the

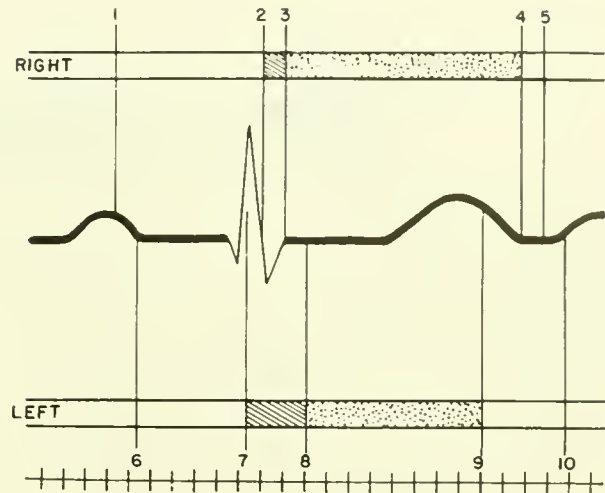


FIG. 18. Schematic presentation of the relationship between electrical and mechanical events. Heart rate 120 beats/min. The markings in lower part of the figure indicate the picture frequency at an exposure rate of 48 frames/sec. 1, Onset of right atrial contraction; 2, onset of right ventricular contraction; 3, onset of right ventricular ejection; 4, end of right ventricular ejection; 5, onset of right ventricular filling; 6, onset of left atrial contraction; 7, onset of left ventricular contraction; 8, onset of left ventricular ejection; 9, end of left ventricular ejection; 10, onset of left ventricular filling. The striped areas represent the phase of ventricular isovolumetric contraction. The stippled areas represent the phase of ventricular ejection. [From Gribbe *et al.* (57).]

cardiac cycle. Figure 19 shows a composite chart made up of superimposed schematized tracings as they are observed in normal man. The chart has been constructed by Agress *et al.* (2) from the most appropriate tracings which they could find in the recent literature. The authors state: "Although this is a composite graph, an accuracy of 0.005 second per scale division was made possible by using a simultaneously inscribed electrocardiogram as the time base." It is evident that claims for an accuracy of 5 msec can be only referred to the electrocardiogram, since the time definition of intracardiac pressure recording through long catheters is usually poorer than 0.005 sec. This fact is not pointed out in criticism of the well-deserving attempts to correlate the various events of the cardiac cycle in man, but only for the purpose of cautioning against hasty conclusions.

Agress *et al.* (2) divide the cardiac cycle into phases, which differ slightly from those customarily accepted in the past. The curves (fig. 19) are intersected by vertical lines based on the time relation of left atrial and left ventricular pressures, as indicated by the upper margin band, *L*, of the graph and the small heart schemes above it. The phases are labeled

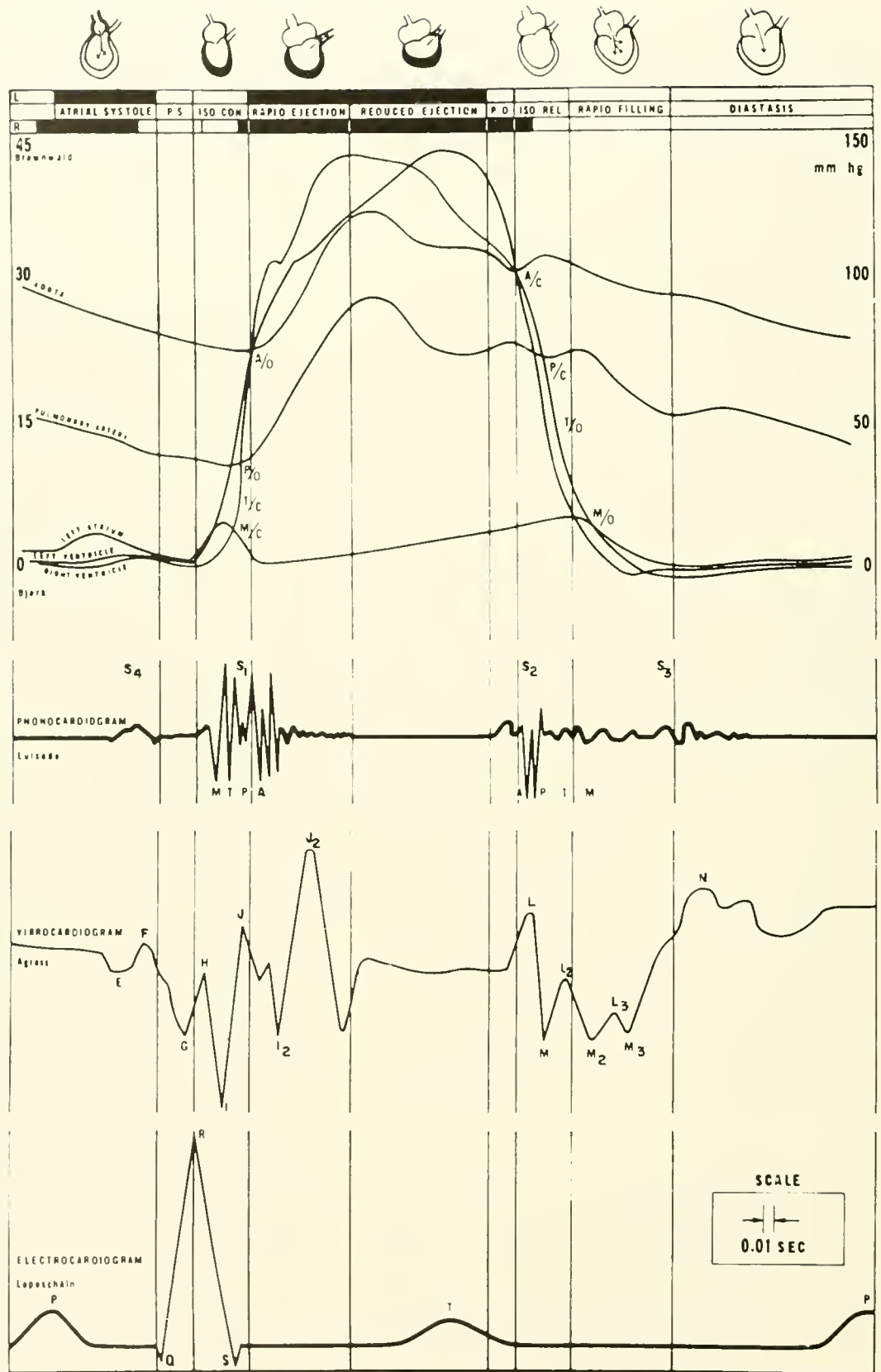


FIG. 19. Composite graph of the events of the cardiac cycle in the human heart. For discussion see text. [From Agress *et al.* (2).]

in the next lower band, where *P.S.* stands for protosystole and *P.D.* for protodiastole. The lowest band of the upper margin, *R*, illustrates the time difference between the activities of the right and left heart. A number of points warrant brief comments. For all intracardiac and arterial pressures a common zero is used. The "low" pressure events (left atrium, right ventricle, and pulmonary artery) are plotted on a scale from 0 to 45 mm Hg (left), whereas the "high" pressure events (left ventricle and aorta) are graphed on a scale from 0 to 150 mm Hg (right). The use of two different pressure scales for correlating simultaneous events on the same time basis results in different slopes. The casual viewer may hastily conclude that the rate of pressure rise during isovolumetric contraction is greater in the right ventricle than in the left ventricle, which is actually not the case. Correspondingly, the pressure drop during ventricular isovolumetric relaxation appears to occur faster on the right than on the left side, which does not happen either. The ascending limbs of the aortic and pulmonary arterial pressure curves have been obtained from overdamped recording systems, such as often happens with long catheters. This might explain why the tracings of the arterial pressures have gentle slopes and remain considerably below the summits of the ventricular pressure curves. An interesting innovation is the protosystolic phase (*P.S.*) which apparently extends from the leveling off of the left atrial A wave until the beginning of the left ventricular pressure rise. It seems to correspond to the conventional Z point. According to the tracings in figure 19, the protosystolic phase appears to be timewise closely related to the electrocardiogram. It seems to last from the beginning of the Q wave until the tip of the R wave. The usefulness of introducing this distinctly different phase seems to lie in the easy correlation of certain characteristics of the phonocardiogram and vibrocardiogram with the cardiac cycle during this time interval.

A number of other cyclical events occurring in the circulatory system also can be more or less accurately correlated with the cardiac cycle. Examples would be: various peripheral arterial and venous pressure pulse curves as well as flow pulse curves; intramyocardial pressures (96); the ballistocardiogram; electrokymogram (42, 163, 135); angiokymogram (147); angiocardiogram; cardiorheogram (3, 68); and heart sounds [Luisada *et al.* (105)]. In all cases the previously mentioned difficulties in precise timing must be given serious scrutiny. A discussion of all

events which lend themselves to correlation would exceed the scope of this chapter.

FUNCTION OF THE HEART VALVES

Valves are essential for efficient action of all reciprocating pumps in order to maintain unidirectional flow. Valves must offer a minimal impedance to flow, yet be able to close abruptly with minimal leakage and minimal displacement. The heart differs from a mechanical pump in that a perfect seal must be obtained in orifices which are continuously changing in shape, size, and position throughout the cardiac cycle. Therefore, the valves must be somewhat larger than the area to be covered in order to remain competent under all normal working situations. The heart valves are also located in orifices beyond which the blood enters wider chambers. This provides for a rapid stream along the axis of the orifice, with decrease in lateral pressure at, and just beyond, the restricted valvular plane (Bernoulli effect) and possibly the production of eddy currents. This mechanism keeps the valves floating in the blood stream and insures rapid approximation of the valve leaflets as soon as the axial stream of blood ceases.

The movements of the atrioventricular and semilunar valves are passive since the valve leaflets do not contain muscle fibers [see also Moritz (116)]. The consideration of this aspect is important because it is easier to replace passive structures by prostheses than it is to create prostheses for active structures such as muscles. It is also possible to investigate the forces involved in the movement of passive structures by observing the function of a prosthesis which simulates a natural organ in suitable physical analogues. Davilla (36) summarizes this trend of thought as follows: "The most successful prostheses have been those which fulfill a passive role in the functional complex: a metal plate on the skull, a nail in a long bone, steel or plastic mesh in a weak abdominal wall, a tube of cloth to replace a blood vessel. . . . Fortunately, the role of the cardiac valves in hemodynamics is a passive one. They are not parts that move but parts which are moved. Their role is identical to that of a simple check valve. It is their environment which complicates the matter. They are immersed in flowing tissue which is chemically unstable but which must not be subjected to extreme unbalance; which possesses a clotting mechanism that must not be activated by the valve; and which transports vital cells that

must not be traumatized. The valves must open and close an orifice which continuously changes in size and provides scant room for support between pulsatile and irregular chambers. The motion of the valves depends upon cardiac action and must be coordinated with those structures which impart it. And, finally, the valvular apparatus must withstand the stress of beating more than forty million times a year during the life span of the subject."

In a multichambered pump such as the heart, valves or valve-like mechanisms are expected at each boundary between functionally separate chambers. We shall therefore discuss the function of the structures which prevent backflow: *a*) at the veno-atrial junction; *b*) at the atrioventricular junction; *c*) at the ventricle-arterial junction.

Veno-Atrial Junction

In adult mammals the sinus venosus is completely incorporated in the atrium and there are only remnants of "valves" which are incapable of preventing backflow into the superior caval vein (valvula Eustachii) or in the coronary sinus (valvula Thebesii). In the left atrium there is not even the most rudimentary valve to prevent backflow in the pulmonary veins. Nevertheless, there are some structures which may contribute to prevent backflow from the atria, such as circular muscle fibers around the pulmonary veins and the coronary sinus, and a complex system of more or less discrete muscular bundles around the orifices of the caval veins. It has been speculated that these fibers contract very early in atrial systole and that by a narrowing of the orifices a valve-like or sphincter-like action occurs [see also Kjellberg & Olsson (91), Burch & Romney (28), Campeti *et al.* (30)]. This would prevent or at least diminish backflow of blood from the atria into the venous trees at the beginning of atrial systole. Although backflow from the atria into the caval veins can be frequently observed and quantitatively registered with flowmeters (18) and contrast media (14), the amount of backflow is surprisingly small as compared to the amount of blood simultaneously pushed by the atria into the ventricles. The precise mechanism by which backflow is kept so small is still enigmatic (144). An interesting light has been cast upon this problem recently by Little (101). He determined pressure-volume curves in the left atrium of dogs during temporary ventricular asystole. His findings suggest that upon a slight rise in atrial pressure above the pulmonary venous pressure there is a closure of the

pulmonary veins near their atrial junction. This closure, apparently brought about by collapse of the vein in a critical region, prevents regurgitation of blood from the atrium into the pulmonary bed. However, at high atrial pressures the closed segment opens and blood flows into the pulmonary veins.

Atrioventricular Valves

The atrioventricular valves are funnel-shaped structures inserted on a fibrous ring. They are developed as an ellipsoidal diaphragm and separated by commissures into somewhat independent cusps, the edges of which delineate the valvular orifice (37, 38). The commissures do not extend all the way to the valve ring (see fig. 3). Traditionally, one distinguishes two cusps on the mitral valve and three on the tricuspid valve, although both valves essentially consist of two large opposite cusps and a variable number of small intermediate cusps at each end of the ellipse [see also Rusted *et al.* (140)]. The strands of collagenous fibers known as chordae tendineae extend from the papillary muscles either to the free edge of the cusps (first order chords) or to a few millimeters beyond the edge (second order chords), or even quite far back into the substance of the valve through a kind of "goose foot" forked insertion (third order chords). The anatomy of papillary muscles is quite variable. One usually recognizes in the right ventricle three groups of papillary muscles to which the tricuspid valve is fastened, whereas there are usually two such groups to fulfill the corresponding function in the left ventricle. The chords are of unequal length, so that probably the same tension is exerted on each at the time the valve closes. The chords from adjacent regions of opposite cusps are inserted on the same or adjacent papillary muscles, in order to insure leakproof closure [see also Brandt (15), Hubacher (82)].

The exact mechanism of closure of the atrioventricular valves has been the subject of much debate [Kantrowitz *et al.* (87)]. The old theory of closure mainly by active contraction of the papillary muscles has been abandoned, and the role of active contraction of muscular fibers at the base of the valves just after atrial systole is taken as either minor, or nonexistent [see also Little (100)]. The decisive factor is probably the onset of ventricular contraction, which establishes a higher pressure in the ventricle than in the atrium. It can be shown that whenever the ventricles begin to contract, there is a retrograde

flow of blood toward the atria which catches the valves like a pair of sails and flings them into apposition. As pointed out by Rushmer (139) this mechanism inevitably involves a leak before the orifice is closed. The occurrence of such regurgitation is widely acknowledged when the atrioventricular valves are closed by a ventricular systole which is not preceded by atrial contraction, i.e., "premature ventricular contraction" [see also Paul *et al.* (128)]. Since the normal wave of excitation propagated by the Purkinje fibers enters the ventricular myocardium over the endocardial surface, at the roots of the papillary muscles, the early contraction of papillary muscles draws the valve edges toward the apex and thereby produces some shortening of the ventricular chamber with a resulting passive lateral displacement of the ventricular walls. During ventricular ejection, the decrease in ventricular volume is accompanied by a further shortening of the papillary muscles, taking up any slack in the valves which might develop.

It has been suggested that under normal conditions, the valves approximate, i.e., begin to close before the onset of ventricular contraction, although it is difficult to substantiate this view by chronologically precise measurements. Many explanations have been advanced for this: passive, upward movement of the valves at the end of diastole caused by retrograde flow of blood along the ventricular wall, or by elastic recoil of the ventricular wall to the strain of atrial systole (8); eddy formation beyond the valves during atrial systole (102); or development of a wave of negative pressure as atrial inflow abruptly ceases [Henderson & Johnson (70)]. Through these mechanisms, the atrioventricular valves are approximated or almost closed just before ventricular systole. Then, when the ventricular myocardium contracts, the valves are completely closed to prevent backflow into the atria.

The concept of a presystolic approximation of the atrioventricular valves received considerable impetus when Dean (37) succeeded in obtaining direct recording of the valve movement in an isolated, surviving heart. Dean demonstrated that when the interval between atrial and ventricular systole is sufficiently long, there is indeed a rapid movement of the valves toward the atrium at the end of atrial systole, followed by a second period of separation of the cusps just before the onset of ventricular systole. When the period of ventricular filling is shorter (at faster heart rates) there is no time to observe separately the effects of atrial systole and of ventricular systole. Then there is "only a single closure move-

ment beginning before ventricular systole, a single movement due in part to auricular contraction and in part to ventricular contraction" (37).

The extent to which the valves and their attachments move in the intact organism has been recently questioned by Rushmer (139). Having observed that exposed or excised hearts tend to shrink, he and his associates surmised that the valves might have much less slack under their normal operating conditions than reported by previous investigators. They used cinefluorography to observe the movements of the mitral valves which had been marked with tiny metal clips at a previous operation. These studies demonstrated that the excursion of the valves, at least where the metal clips were placed, toward the atrium is remarkably small, and pointed to a more or less continuous restraint by the chordae tendineae.

Arterial Valves

The aortic and pulmonary valves consist of three symmetrical cusps attached, similarly to suspension bridges, around the circumference of the valve orifice (see fig. 3). When the cusps are approximated they form a starlike figure; when open, they delineate a nearly rounded but still somewhat triangular orifice of an area slightly smaller than that of the artery. At the tip of each triangular valve leaflet, where the three valve leaflets come in contact, there is a discrete thickening called the nodulus Arantii. There are also thin, membrane-like structures (lunulae) on the free edges of the valves on either side of the noduli. Normally the free edges come into contact surface against surface rather than border to border. Toward the valvular orifice, the ventricular musculature assumes the shape of a funnel (*conus arteriosus*), whereas beyond the valves at the origin of the aorta and pulmonary artery there are three outpouchings which provide some free space behind the valve cusps even when they are maximally opened.

The mechanism of action of the arterial valves can be described as follows. During ventricular ejection, the blood stream opens the valves from below and a rapid flow is established along the axis of the valvular orifices. However, the valves are not pushed flush against the arterial wall. On the contrary, eddy currents, generated by the axial jet of blood, swirl in the spaces behind the cusps. Indeed, the action of turbulent eddies is such that the faster the ventricular ejection, the closer to the center of the axial stream the valve edges are brought [Hochrein (76)]. Thereby the valves are prepared to close almost instantane-

ously as soon as ventricular ejection ceases. It is likely that contractions of muscle fibers in the conus arteriosus tend to make the valve rings more narrow during ejection, as discussed in an earlier section. In this manner axial velocity of flow is increased and turbulence, which may prepare the valves for closure, is enhanced. At the end of systole when ejection ceases, the forward movement of blood in the root of the artery continues for a very brief period. Then, the action of the eddies on the upper surface of the valves prevails over the force exerted from below (rapidly falling intraventricular pressure). Hence the retrograde surge of blood toward the ventricle (see fig. 15) is arrested by valve closure, and marked pressure differences between the relaxing ventricle and the elastically distended aorta can develop.

VENTRICULAR AND ATRIAL VOLUMES IN VARIOUS ACTIVITIES

Certainly one of the most important features of a pump is the volume which can be propelled per stroke. This is easy to measure in a mechanical pump, but it requires complex and sophisticated instrumentation to determine the stroke volume of the intact heart. Successful attempts in this direction have recently been reported, e.g., by Rushmer (139) and his school, by Hawthorne (67), and by Olmstead (personal communication). Nevertheless, numerous questions remain still unanswered, namely, *a*) the quantitative correlation of the stroke volume with the other parameters of cardiac activity, and *b*) the relationships of the ventricular stroke volume to the volumes remaining in or passing through the atria, the ventricles, and the large vessels. At the present time most of these questions can only be approached under highly controlled situations which limit the significance of the experiment. Discrepancies are therefore encountered depending upon the method of approach used. At this point, it must also be remarked that heart volumes have traditionally been measured by X-ray or cardiometer techniques which include the volumes of the walls. Only recently have radiopaque dyes and other media been developed which permit measuring the content of the cardiac cavities and not their over-all volumes (56). Consequently a large part of the data incorporated in the literature require critical attention. In this chapter, the word "volume" refers exclusively to the liquid content of the cardiac cavities and excludes the volume oc-

cupied by the walls and by the blood-filled vessels or channels in the walls.

Ventricular Volume

To describe the changes in ventricular volumes under dynamic conditions, it is advisable to review the modern terminology introduced by Rushmer (139). This terminology is illustrated and somewhat expanded in figure 20 by drawing a parallel between the familiar lung volumes (left) and the ventricular volumes (right).

The stroke volume of the organism at rest corresponds to the tidal volume of respiration. In exercise the ventricle can also eject some of the blood which at rest would remain in the ventricular cavity at the end of systole. Rushmer suggests the term "systolic reserve volume" for that additional amount of blood which is not ejected under resting conditions, but can be maximally ejected with a more forceful contraction. This corresponds to the expiratory reserve volume of the lungs. The volume of blood left in the ventricle after a normal systole used to be called "residual volume." Rushmer restricts the term residual volume to that amount of blood remaining in the ventricle after maximal ejection. Then the term corresponds truly to the lung residual volume. The ventricle can also increase its stroke volume by an augmented venous return during diastole and subsequent ejection of this extra volume in addition to the resting stroke volume. The term "diastolic reserve volume" defines the maximal amount of blood which the ventricle can receive and then eject in addition to the normal diastolic inflow. This volume corresponds to the inspiratory reserve volume of the lungs. The resting stroke volume, systolic reserve volume, and diastolic reserve volume together define the maximal stroke volume, which corresponds to the vital capacity of the lungs.

The parallelism can be carried even further (fig. 21). In the resting organism, the amount of blood remaining in the ventricle at the end of ejection (called by some authors the "end-systolic volume") would best be referred to as functional residual capacity since it is now customary to use the term capacity for the sum of two or more "volumes." ("Capacity" does not imply something that is absolute or fixed, despite the unfortunate analogy suggested by the age-old and uneradicated expression "vital capacity.") The functional residual capacity of the ventricle comprises the systolic reserve volume plus residual

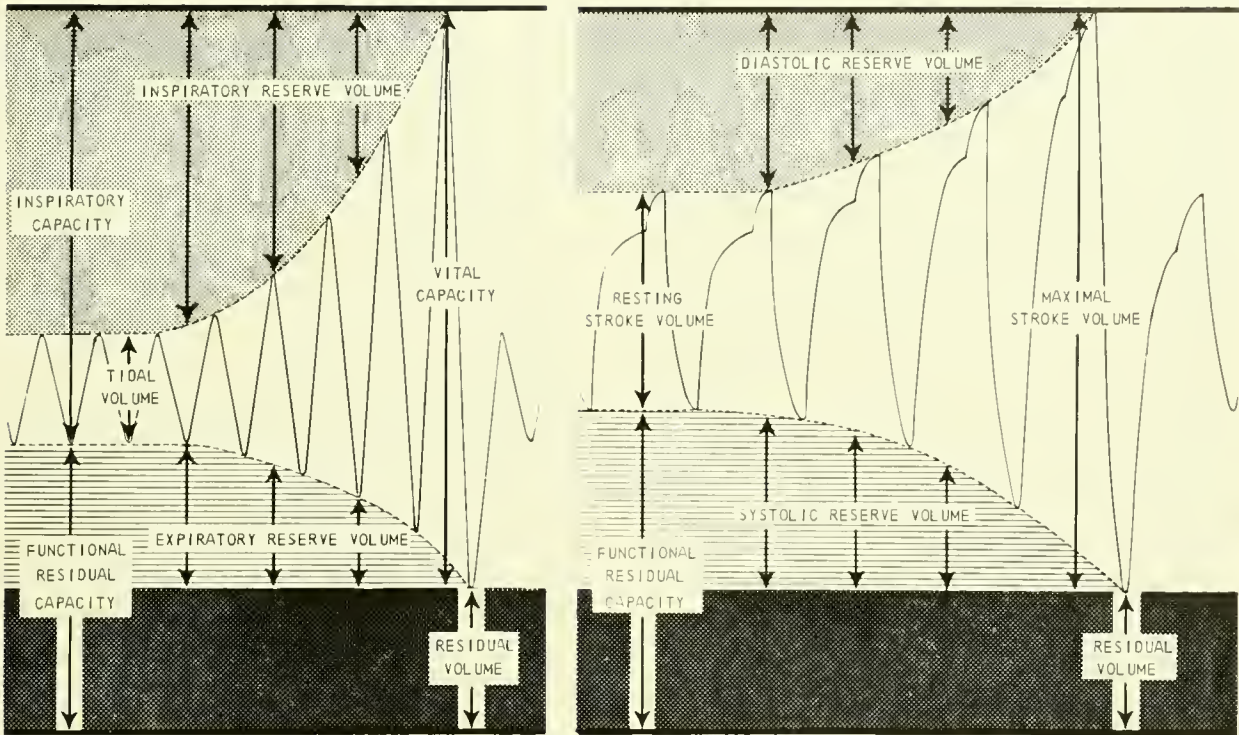


FIG. 20. Scheme of lung volumes (*left*) and ventricular volumes (*right*) at rest and during exercise or sympathetic stimulation. For details see text.

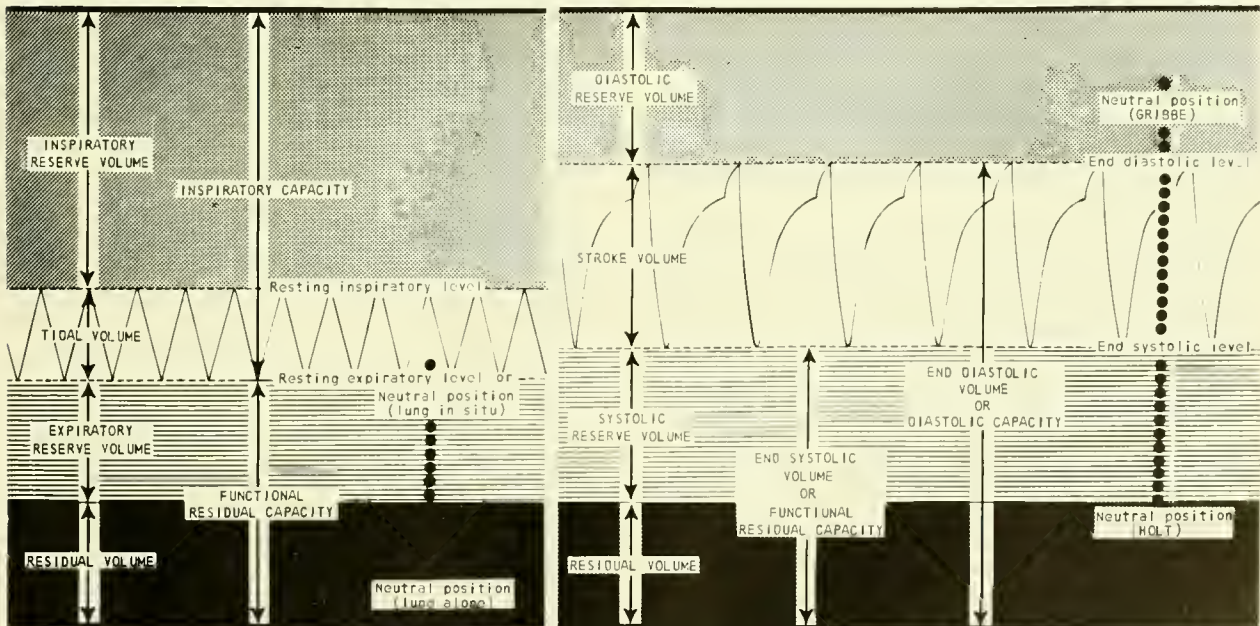


FIG. 21. Scheme of lung volumes (*left*) and ventricular volumes (*right*) at rest to illustrate the parallelism between respiratory and ventricular volumes.

volume, much as the functional residual capacity of the lungs comprises the expiratory reserve volume and the residual volume. Correspondingly, the amount of blood accumulated in the ventricle at the end of ventricular diastole (often called the end-diastolic volume) could be referred to as "diastolic capacity," including the stroke volume plus systolic reserve volume plus residual volume. Since the stroke volume varies with changes in activity, the diastolic capacity is not a fixed amount but functionally variable. It becomes larger as the stroke volume increases and smaller as the stroke volume decreases. There are two more terms which can be described in parallelism with the nomenclature used in respiratory physiology. The volume level reached at the end of systolic ejection is termed "end-systolic level" and corresponds to the expiratory level of the lungs. The volume level reached at the end of diastolic filling is called "end-diastolic level" in analogy to the inspiratory level of the lungs.

The importance of a clear terminology for the description of the dynamic shifts of ventricular volumes under varying conditions of activity has been pointed out by Rushmer (139) and many others have followed his lead. The parallel with the lung volumes also permits useful analogies. For instance, an increase in residual volume of the lungs in emphysema diminishes the ventilatory efficiency. In a somewhat similar manner an increase in the ventricular residual volume, such as occurs in excessive ventricular dilatation, diminishes the pumping efficiency of the heart.

To compare with the cardiac ventricles, a piston pump would need the following features. The course of the piston, which defines the stroke volume, would have to be limited in order to leave fluid in the pumping chamber at the end of ejection (functional residual capacity). If a greater output were needed, the piston would have to push farther and increase its stroke volume by encroaching upon the systolic reserve volume. Yet the volume filling the dead space of the pump (residual volume) could never be ejected. The diastolic reserve volume would be represented by a farther pulling back of the piston to allow greater filling of the pump chamber. In this mechanical system, the need for a greater output could be met instantaneously by the ejection of part of systolic reserve volume. However, the diastolic reserve volume could not be utilized instantaneously because the pump chamber has first to be filled to a greater extent before more can be ejected. The situation seems to be the same in the heart. The left ventricular

stroke volume can be increased from one heart beat to the next by drawing upon the systolic reserve volume, as occurs for instance when the organism passes abruptly from rest to exercise (33, 139, 146). On the contrary, the mechanism of greater diastolic filling (Starling's law) always involves a brief delay brought about by the need for greater venous return before increased ejection. Apparently, only in strenuous exercise and in some pathological conditions is the diastolic reserve volume called upon.

Indeed the ventricular stroke volume varies almost continuously and is not identical from beat-to-beat even under resting conditions. Some of the variations are probably caused by the fluctuating play of poorly known neural feedback processes. Others are caused by mechanical forces such as those which accompany respiration. In fact the respiratory variations of the ventricular stroke volume are remarkable even under resting conditions (21). Figure 22 shows the typical changes in right ventricular output during five heartbeats modified by the action of one respiratory cycle. After the onset of inspiration, *A*, there is first an increase in venous inflow (second heartbeat) and then in ventricular stroke volume (third heartbeat). Similarly, the drop in venous return during expiration (at the fourth heartbeat) is reflected by a decrease in stroke volume one beat later. From this record it appears that the right ventricle temporarily accommodates part of the large inspiratory inflow of venous blood, and releases it into the pulmonary circulation during the respiratory pause. This indicates that with respiration not only the stroke volume varies but also the functional residual capacity (or end-systolic level).

The functional residual capacity cannot be measured directly in the intact organism. Most of the estimates obtained with indirect methods display considerable variation according to the technique employed. The volume curves shown in figures 16 and 17 were obtained with multiple plane high-speed X-ray cinematography. They show not only the volume changes throughout the cardiac cycle, but also the end-systolic level. The functional residual capacity of the left ventricle of these 12-kg dogs amounts to approximately 5 to 6 ml. In unanesthetized, quiescent dogs, the values measured were of the same order of magnitude. Gribbe *et al.* (56, 57) estimate that on the average the stroke volume of dogs is 60 per cent of the diastolic capacity. Thus functional residual capacity amounted to 40 per cent of the diastolic capacity. It should be pointed out that Gribbe's values are much smaller than the

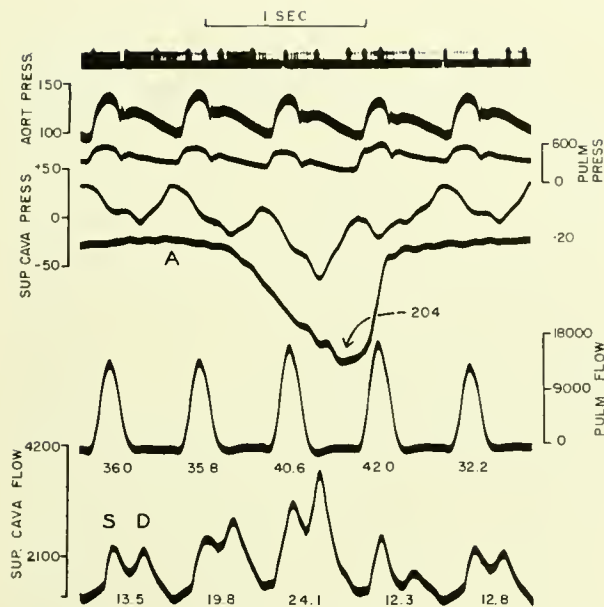


FIG. 22. Effect of spontaneous respiration on right ventricular stroke volume, measured by the directly recorded pulmonary blood flow in an anesthetized normal dog. The simultaneously recorded pattern of right atrial filling (represented by superior vena cava flow), arterial, venous, and intrathoracic pressures permit a time correlation. Tracings from top to bottom: time and base line, aortic pressure in mm Hg, pulmonary artery, superior vena caval and intrathoracic pressures in mm water, pulmonary arterial and superior vena caval flows in ml/min. *A* = beginning of inspiration; *S* = acceleration of superior vena caval flow during ventricular systole; *D* = acceleration of superior vena caval flow during ventricular diastole. Stroke volume (in ml) entered under pulmonary artery flow curve. Flow (in ml) through superior vena cava during each cardiac cycle entered at bottom of record. Electrical frequency response of both flowmeters reduced from 400 to 40 cycles/sec. Superior vena caval pressure curve damped. [From Brecher & Hubay (21).]

estimates of Holt (77) with dye dilution techniques, which range from 30 to 76 ml for a dog of 15 to 16 kg in weight. This enormous discrepancy cannot be reconciled at present. Simultaneous determinations under rigidly controlled conditions with both methods, the cineangioradiography and the indicator dilution technique, may elucidate this point.

That the situation is equally unsettled for measurements in man is shown by the work of Rushmer (139), Chapman *et al.* (32), Nylin (122), Reindell *et al.* (134), Folse *et al.* (47), Lüthy (personal communication, and 106). Generally, determinations using roentgenologic technique furnish smaller values for the functional residual capacity than measurements with dye dilution techniques. For instance, Folse *et al.* (47), employing radio-iodinated Diodrast, found in 20 resting persons that the left ventricular

stroke volume averaged 42.2 ± 8.8 ml per m^2 of body surface area. The diastolic capacity averaged 90 ± 26 ml per m^2 (functional residual capacity 48 ml/ m^2). On the other hand, Lüthy (106) found with thermodilution techniques that in normal patients the left ventricular stroke volume amounted to 45 ml per m^2 of body surface (range 39–57 ml/ m^2) but the diastolic capacity to 145 ml per m^2 (range 128–173 ml/ m^2). According to these data the stroke volume would be only one-third of the diastolic capacity [39%, Folse *et al.* (47); 31%, Lüthy (106)] whereas, in the dog it is apparently about two-thirds (60%, Gribbe).

The problem is further complicated by the fact that the ratio of stroke volume to functional residual capacity changes markedly under various normal and pathological conditions. This is well illustrated by the observation that a great increase in resistance to ventricular ejection (e.g., in extreme hypertension) causes the heart size to become much larger while the stroke volume decreases. This implies a large increase in the functional residual capacity. Direct evidence for an increase in functional residual capacity under this condition is the observation that, when the aortic resistance is suddenly reduced by opening of an arteriovenous shunt, the first stroke volume is twice the normal size [Hamilton (61)]. From the foregoing it is obvious that much more information based on direct measurements of heart volumes under various conditions is needed.

Atrial Volume

The volume of blood contained in the atrium at any time has evoked much less interest than the ventricular volume. No quantitative information has been available until recently. Even the terminology of atrial blood volumes is more difficult to define than that of ventricular volumes. During two phases of the cardiac cycle (isovolumetric contraction and isovolumetric relaxation), the ventricle contains a definite volume because the atrioventricular and semilunar valves lock the ventricular content. The atria, however, are always open on the venous inflow side. On the outflow side they are closed only from the beginning of isovolumetric ventricular contraction to the end of isovolumetric ventricular relaxation. Consequently, the volume contained at any one instant represents the balance of almost continuously changing inflow and outflow.

The changes in atrial volumes can be understood by following the atrial volume curves (open circles)

in figures 16 and 17. The left atrial volume is greatest during isovolumetric relaxation of the left ventricle. During the rapid ventricular inflow phase the atrial volume decreases rapidly, but not so fast as the ventricle fills. This indicates that some blood enters the atrium from the veins while at the same time a greater amount leaves it toward the ventricle. During the phase of slow ventricular inflow (diastasis) the atrial volume remains practically unchanged, pointing out that inflow from the veins and outflow toward the ventricle are approximately in balance. Incidentally, this gives a measure of the rate of venous return to the atrium during this phase by simply calculating the increase in ventricular volume. During atrial systole (approximately end of P wave of electrocardiogram, fig. 17) the atrial volume decreases precipitously. The rate at which the atrial volume decreases and the ventricular volume simultaneously increases speaks in favor of a negligible backflow of atrial blood into the veins during atrial systole. At the peak of atrial systole the volume of blood contained in the atrium is minimal, but still amounts to approximately 4 ml in dogs. During the phase of isovolumetric ventricular contraction, the atrial volume already begins to increase owing to an accelerated venous inflow. It continues to increase at a rather fast rate during rapid ventricular ejection and at a slower rate during the phase of reduced ventricular ejection. Whereas the ventricular stroke volume of the 12-kg dog amounts to about 8 ml, the difference between the largest and smallest atrial volume amounts to only 5 ml. This indicates that during the ventricular rapid and slow filling phases approximately 3 ml passes from the veins through the atrium into the ventricle without being recorded as an atrial volume increase. It further indicates that during ventricular isovolumetric contraction, rapid and reduced ventricular ejection, about 5 ml pass from the veins into the atrium while the atrioventricular valves are closed.

Obviously, one expects during exercise a greater accommodation of blood in the atrium during ventricular ejection and a greater outflow of blood from the atrium into the ventricle during the ventricular rapid and slow filling phase. There are still no measurements available concerning such physiological adaptations. It appears reasonable to suggest that in exercise the atrium ejects during its own systole a greater volume, thereby drawing upon the amount of blood usually remaining at rest in the atrium at the end of atrial systole. This might be termed the "atrial systolic reserve volume."

ATRIAL FILLING

The phasic changes of venous return which bring about atrial filling are still a subject of debate. It is often stated that venous blood returns to the heart solely as a result of the force imparted to it on the arterial side of the circulation (*vis a tergo*). Yet there are reasons to believe that the systolic contraction of the ventricular myocardium also contributes to atrial filling by causing an expansion of the atria [see also Hamilton (60) and Holzlöhner (79)]. This view was originally advocated by Purkinje (132) who observed that during ventricular systole the atrioventricular junction (the plane of the heart valves) descends toward the apex and pulls on the atrial walls. The atrial cavity is then passively expanded and the pressure in it drops, causing an acceleration of blood from the veins into the atria. Among functional anatomists, the concept of the attraction of blood into the atrium by the descent of the valvular plane toward the apex during ventricular systole has gained great favor. By injecting drops of radiopaque contrast material into peripheral veins and taking X-ray cinematographic pictures, Böhme (14) could demonstrate a remarkable acceleration of central venous flow during ventricular systole. Records obtained from direct measurements of blood flow in the superior and inferior venae cavae with a high fidelity flowmeter by Brecher & Praglin (25) and by Brecher (19) confirmed Böhme's observations. It appears now that ventricular contraction does cause a sudden expansion of the atrium. This mechanism lowers the pressure in the atrium and produces the X wave, much as a plunger withdrawn in the barrel of a syringe lowers the pressure therein. The expansion of the atrium probably begins with the asynchronous contraction of the papillary muscles during the early part of the isovolumetric phase and continues during rapid ventricular ejection. In the hands of Rushmer (136, 139) the lipiodol injection technique indicated only a moderate acceleration of caval blood flow during early ventricular systole [see also Lynch (107)]. However, Rushmer's findings can be reconciled with those of Böhme and Brecher, if one considers the differences in the various experimental conditions (open or closed chest, anesthetized or awake animals, slow or fast heart rate, inspiration, expiration, volemic status, etc.). The measurements of Gribbe (56, 57) in intact closed-chest animals definitely indicate an increased atrial inflow beginning at isovolumetric ventricular contraction and continuing during the rapid phase of

ventricular ejection (see atrial volume curve in fig. 16 and superior vena cava flow curve in fig. 22). In Chapter 17, vol. I, of this *Handbook*, evidence is given that in normal man the venous stream toward the heart pulsates reciprocally to the aortic stream leaving the chest. The exactitude of the reciprocal relationship is said to be measured by the very small volume equivalent of the cyclic changes (cardiac) in intrathoracic pressure after making allowance for the elasticity of the chest walls (60, 64).

In conclusion, the filling of the atrium during ventricular systole depends not only upon the pressure of blood in the venous reservoir which is available for passive filling from behind; it depends also on the vigor with which ventricular systole moves the atrioventricular junction. Thus a more forceful contraction (commonly associated with a larger stroke volume) ensures additional inflow into the atrium and therefore facilitates the next ventricular ejection without the need for further decreasing the systolic reserve volume to maintain a large stroke volume. The increase in ventricular outflow and in atrial inflow are mediated by the same force, ventricular contraction, and both favor a more thorough filling of the ventricle during the next diastole.

The central veins are most suitable for this reservoir function because through partial collapse of their walls, their content can change rapidly without much change of pressure. They form a collapse chamber which is the functional counterpart of the aortic compression chamber (18). On the arterial side, the compression chamber based on the elastic distensibility of the walls assures the transformation of the discontinuous cardiac ejections into steady flow to the tissues. On the venous side, the collapse chamber based on the pliability of the walls assures at the atrial entrance the transformation of the steady flow from the tissues into the pulsatile flow which is needed for the discontinuous cardiac filling [see also Irisawa *et al.* (83)].

The filling of the venous collapse chamber is in turn aided by the atrial systole. From a hemodynamic standpoint the function of atrial contraction is two-fold: 1) It ejects some blood into the ventricular cavity, a well-established fact, and 2) it passively enlarges the central venous reservoir by briefly slowing down or stopping atrial inflow. The small amount of backflow which is often recorded during atrial systole at the caval-atrial junction normally does not extend far into the periphery (18). It is readily taken up by a widening of the collapse chamber and, together with the continued inflow

from the periphery, creates the pool from which the next ventricular filling derives its supply.

Any force which lowers pressure in a region toward which flow occurs, is called suction, whether or not the pressure developed in that region drops below atmospheric zero. Physically "suction" is the same as pressure (force per area). It is a reduction of pressure at some point in a system by the application of a force which results from an energy conversion process, e.g. muscular contraction, elastic recoil, pulling of a plunger. Since blood is attracted into the atrium by ventricular contraction, one may therefore state that atrial filling is at least in part brought about by suction upon the venous blood mediated through a stretching and enlargement of the atrial cavity by the contracting ventricular muscles which cause a descent of the atrioventricular junction. This phenomenon can be termed "ventricular systolic suction" upon the atrial content.

[A semantically more rigid definition of the concept of "suction" holds that suction can be thought of only in locations where the transmural pressure is negative (142). Accordingly suction cannot be transmitted through viscera (atria, veins) which have collapsible walls. As long as these viscera contain blood at a greater pressure (including equivalent kinetic energy) than the extra visceral pressure, the dominant force is "pressure" from upstream rather than "suction" from downstream. This pressure maintains the walls of the atria and intrathoracic veins under elastic tension during the entire cardiac cycle. Ed.]

When the atrioventricular valves open during ventricular diastole, there is another decrease in atrial pressure (Y wave), which results once more in an acceleration of venous blood inflow into the atrium. This second acceleration is more pronounced at slow heart rates and is usually greater in closed-chest than in open-chest animals. Apparently the expansion of all the cardiac cavities through the pulling force of the lungs [Pfuhl (129, 130)] helps to make the atrial inflow during ventricular diastole slightly greater than during ventricular systole. The increase in atrial inflow during ventricular diastole may also be a consequence of the attraction of atrial blood into the ventricle through the forces which expand the ventricle during diastole (ventricular diastolic suction, see following section). These forces not only affect the blood contained in the atrium but in turn even affect the adjoining veins by lowering the atrial pressure, particularly during the phase of rapid ventricular filling. Figure 22 illustrates the phasic increases in superior vena caval flow during ventricular systole (S) and during ventricular diastole (D) in an anesthetized closed-chest dog.

In summary, ventricular myocardial contraction could have a threefold effect upon atrial filling: 1) It imparts so much energy to the arterial stream that even after passing through the capillaries, the blood continues to flow in the veins and fills the central reservoirs; 2) during ventricular systole blood is drawn actively into the atrium through an expansion of the atrial cavities by a movement of the atrioventricular junction toward the apex ("ventricular systolic suction"); 3) during ventricular diastole the elastic forces, created by the preceding systole in the ventricular walls, can aid in drawing blood from the atrium into the ventricle and even in attracting blood from the veins into the atrium ("ventricular diastolic suction" upon the atrial content).

VENTRICULAR FILLING

While the forces causing ventricular ejection are unquestionably those originating from myocardial contraction, there is considerable debate concerning the forces responsible for ventricular filling [for details see Brecher (19), Krug & Schlicher (95), Eldridge & Hultgren (41), Bauereisen *et al.* (7)]. The ejection of fluid from a pump is more spectacular than the filling phase. This may be the reason why the forces dealing with ventricular contraction have received considerably more attention than the forces dealing with ventricular filling. For a long time it has been believed that the heart is filled exclusively by a force which pushes blood into the ventricle from behind [*vis a tergo*, Galli (50)]. This force results from the preceding ventricular contractions and is imparted to the blood for circulating it through the arteries, capillaries, and veins. Others have maintained that some part of ventricular filling is produced by a force from the front (*vis a fronte*) which attracts or sucks blood from the atrium into the ventricle. This force would manifest itself in the ventricle during diastole and would probably be caused by an elastic recoil of the ventricular walls. It would lower the intraventricular pressure below the level which would prevail if such a *vis a fronte* did not exist. The history of the issue between *vis a tergo* and *vis a fronte* is treated in detail by Ebstein (40), Hamilton & Lombard (64), Böhme (14), Brecher (19, 20), Krug & Schlicher (95). One can summarize as follows the evidence in favor of the existence of a *vis a fronte*: Ventricles of cold-blooded animals, in the observations of Kraner & Ogden (94), Kraner (93), Hennacy & Ogden (73), Hennacy (72),

Peiper & Weigand (131), and of mammals according to Bloom (13), Fowler *et al.* (48, 49) Brecher (19), and O'Brien (123), can definitely suck in blood when the filling pressure at the atrioventricular orifice is atmospheric (zero) or subatmospheric (negative). Whether or not ventricular suction also contributes to ventricular filling in the presence of a positive filling pressure at the atrioventricular orifices has not yet been experimentally established.

It has been objected that the ventricles in which suction forces were demonstrated had an abnormally small functional residual capacity. The question therefore arises whether or not ventricles with physiological volumes would also exert a suction force. Scheu & Hamilton (143), using the intact spontaneously breathing anesthetized dog, made simultaneous recordings of the intraventricular and thoracic pressure and thus established the transmural ventricular pressure gradient. They held that "suction," probably by the elastic recoil of the ventricular walls, could be demonstrated only if and when the transmural pressure was negative. They concluded that suction did not occur during normal diastole but could be brought about by compressing the mitral orifice or by hemorrhage. These two maneuvers made the diastolic ventricular shadow smaller and were thought to have reduced the residual blood to a subnormal figure.

Brecher & Kissen (23) demonstrated that dog ventricles of an approximately normal functional residual capacity filled by suction at zero ventricular inflow pressure. Nevertheless, as long as there is not unequivocal experimental proof of the existence of ventricular diastolic *vis a fronte* in the unanesthetized intact mammalian organism, one should be exceedingly cautious with any statement concerning the role of diastolic suction in ventricular filling [Brecher (20)].

Horres and his group (unpublished observations) determined the average left ventricular volumes of excised submerged hearts at equilibrium state and found it to be 17 (± 6) ml for dogs weighing 12 kg (fig. 23). If one assumes that the elastic equilibrium state of the relaxed ventricle *in vivo* is the same as that of the freshly excised, and still responding ventricle *in vitro*, then diastolic ventricular suction could occur at any ventricular volume below the equilibrium point (i.e., less than 17 ml). Unfortunately the values of the functional residual capacity reported for the dog heart vary too much to permit an unbiased conclusion about the role of suction in ventricular filling. According to the data of Holt

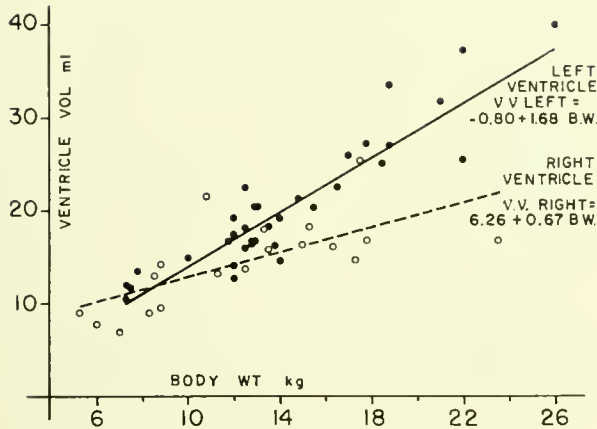


FIG. 23. Relationship of ventricular volume (V.V.) and body weight (B.W.) in dogs. Ventricular volume measured at the equilibrium state (zero transmural pressure). [See also fig. 2 (Horres *et al.*, unpublished observations).]

(77) the average functional residual capacity of the left ventricle would be approximately 30 ml for dogs weighing 12 kg. According to Gribbe *et al.* (57), it is only 5 ml. The discrepancy between Holt's and Gribbe's measurements in terms of ventricular diastolic suction is illustrated in figure 24. If Holt's data are correct, ventricular diastolic suction never occurs under normal conditions. On the contrary Gribbe's figures speak for the occurrence of diastolic ventricular suction during all phases of diastole. Obviously the controversy cannot be resolved on the basis of presently available data.

There has been some speculation about the possible nature of the frontal force, particularly whether it originates from an active or a passive process. An active process would be the contraction of muscle fibers which, owing to their anatomical arrangement, could widen the ventricular cavity during diastole [Guasp (58)]. There is no experimental evidence to support such a view. Another active process would be the development of a force acting to lengthen the muscle fibers upon completion of their contraction ("active decontraction"). However, it has never been satisfactorily demonstrated that processes of energy conversion from chemical to kinetic energy occur during muscular relaxation [Villa (152); for review, Brecher (19, 20)]. The most acceptable evidence is, at present, that the diastolic ventricular vis a fronte is caused by passive processes, such as one of the following. *a*) During systole an interfascicular tension develops through shear forces between myocardial strands which contract to different extents and asynchronously [details in Rushmer (139)]. *b*) During systole noncontractile elements in

the heart and possibly also some components of the muscle fibers are elastically deformed beyond their equilibrium state, thereby storing potential energy which is released through elastic recoil during diastole (see fig. 2). *c*) In the closed-chest mammal, additional external forces residing in the elastic recoil of the lungs exert their effect upon the heart by tending to expand the cardiac cavities beyond the size these cavities would assume in the absence of the lung forces.

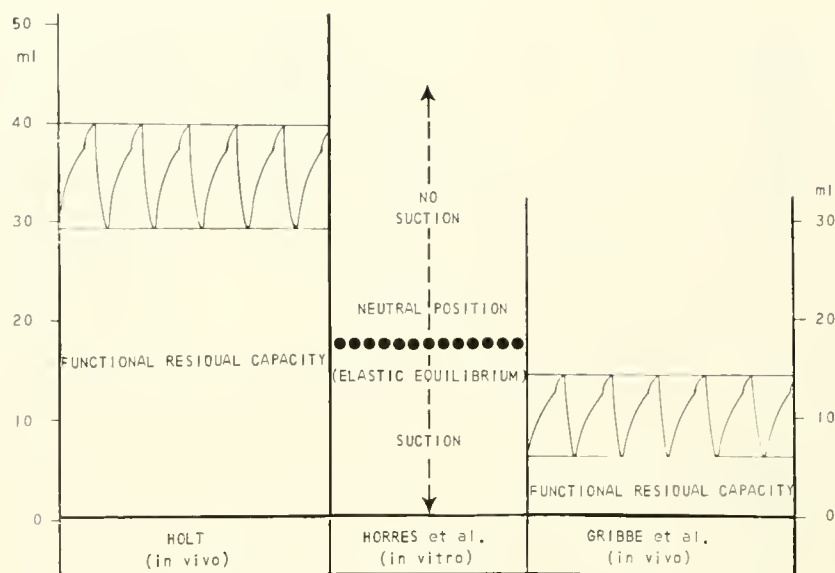
In conclusion, some of the classical views concerning the filling of the heart may need revision. The ventricle acts as a reciprocating pump in which the output stroke simultaneously provides energy for the filling of the pump for the next stroke. In other words, the heart does not act merely as a pressure pump as William Harvey (66) believed, but it actually functions as a pressure-suction pump [see also Gauer, (52, 53)]. The amount of energy necessary for pump filling is, however, only a fraction of that needed for ejection, since the filling occurs through a fluid transfer into a low resistance system in which small pressure differences will cause a rapid flow of large amounts of blood.

DIFFERENCES BETWEEN RIGHT AND LEFT CARDIAC CAVITIES

Functional differences between the right and left cardiac cavities can be expected from their anatomical characteristics. Yet it had long been tacitly assumed that the two atria and the two ventricles initiate and terminate their contraction simultaneously, and that a description of cardiac events on both sides would be redundant.

In fact, there are significant differences between the left side and the right side chambers [see also Katz (89), Hamilton *et al.* (62), Luisada & Fleischner (103), Segers (145), Braunwald *et al.* (16), McKusick (109)]. For instance, at equal pressures the right atrium has a volume twice that of the left atrium, which is thicker and less distensible than the right (99). Experimentally, the volume-pressure curve relationship in the left atrium has been found to be linear only as long as the pressure remains within the normal limits (pressure below 150 mm H₂O). When this limit is exceeded, a slight increase in volume causes a much larger increase in pressure. The normal level and patterns of pressure also differ somewhat between the right and the left atrium. The A wave of the right atrium, produced

FIG. 24. Functional residual capacity of the dog's ventricle and its relation to ventricular diastolic suction. *Left*: data derived from Holt (77), assuming that a functional residual capacity of 50 ml in a 20.9-kg dog corresponds to 30 ml in a 12-kg dog (regression line of fig. 23). *Right*: data of Gribbe *et al.* (56) for a 12-kg dog. *Center*: elastic equilibrium state of the ventricle in a 12-kg dog (Horres *et al.*, unpublished observations).



by atrial systole, is often not so steep and tall as that of the left atrium, and normally precedes it slightly. The peak of the right atrial V wave is usually lower than that of the left atrial V, and the mean right atrial pressure is usually less than the left atrial pressure.

At the level of the ventricles the bundles of myocardial fibers which encircle the two cavities, much as the windings of a turban, belong to a common anatomical structure. The combined effect of their contraction is to wring blood out of the ventricular chambers into the respective arteries. Yet the muscular arrangement is such that contraction of the left ventricle produces primarily a reduction in the lateral diameter with only a moderate shortening along the vertical axis, whereas on the right side there is much ventricular shortening between apex and base with relatively less pulling of the free wall toward the septum. The mechanical effects of left ventricular contraction occur a trifle earlier than those of right ventricular contraction, since the rise in right ventricular pressure usually lags by 0.01 to 0.02 sec behind the rise in left ventricular pressure (see also fig. 19). It is, therefore, understandable that mitral valve closure usually precedes tricuspid valve closure. Nevertheless, it is by no means established whether the later start of right ventricular contraction is the only cause of asynchronicity. Other factors could also operate, such as a faster rate of contraction of the left ventricular wall or a quicker reaction of the mitral cusps to the rising wave of pressure in comparison with the tricuspid valve. The characteristics of the vascular bed into

which ejection proceeds cause differences in the sequence of pumping events on the right and on the left side. Since the pressure in the pulmonary artery is low (low resistance to flow in the pulmonary vascular bed), the pulmonary valve opens first. Indeed, for an interval of about 0.02 sec, the ventricular contraction produces an ejection on the right side while there is still an isovolumetric pressure rise on the left side. Similarly, right ventricular ejection continues well after cessation of left ventricular ejection. In other words, the end of left ventricular systole precedes that of the right and closure of the aortic valve precedes closure of the pulmonary valve. On the other hand, because of a much longer phase of isovolumetric relaxation in the left ventricle as compared to the right, the opening of the mitral valve is thought to follow that of the tricuspid, as seen in table 1, which is borrowed from Luisada & Liu (104) and summarizes the sequence of events of right and left ventricular contraction (see also figs. 18 and 19).

Because of these differences in the pumping action of the ventricles, reference is often made to right and left ventricles as being a "volume pump" and "pressure pump," respectively. Implied in this nomenclature are the facts that the right ventricle can easily handle an increase in volume output without apparent strain, whereas it is not so well equipped for raising its pressure to a high level. On the contrary, the left ventricle, with a much larger mass of active musculature and a more nearly spherical geometry is better able to face an increase in out-flow resistance than the right ventricle. What is

TABLE 1. *The Cardiac Cycle. Time Intervals Between Valvular Motions (Normal Dogs)*

| Event | Interval, in Sec |
|----------------------------------|------------------|
| Q wave (ECG) | 0.06-0.07 |
| Closure of mitral valve | 0.00-0.02 |
| Closure of tricuspid valve | 0.01-0.03 |
| Opening of pulmonic valve | 0.01-0.02 |
| Opening of aortic valve | |
| Closure of aortic valve | 0.02 |
| Closure of pulmonic valve | 0.03-0.04 |
| Opening of tricuspid valve | 0.04-0.08 |
| Opening of mitral valve | 0.00-0.04 |
| Rapid filling of right ventricle | 0.04-0.08 |
| Rapid filling of left ventricle | |

Each peak of rapid ventricular filling follows A-V valve opening by 0.08-0.10 sec, and the closure of the respective semilunar (i.e., pulmonary or aortic) valve by 0.12-0.18 sec. This table shows the sequence of events in normal, large dogs, whose figures are probably very close to those of normal man. [From Luisada & Liu (104).]

meant by the terms "volume pump" and "pressure pump" is actually "low-pressure head pump" and "high-pressure head pump."

There is no fundamental difference in the pumping action of the two ventricles before birth. They both receive blood from a common atrial chamber, their walls are of the same thickness, they have the same capacity, and they both eject their contents into a common aortic chamber via either the ductus arteriosus or the ascending aorta. The pressure against which the fetal ventricles eject their contents is lower than that in the adult systemic circuit, but after birth the resistance in the lesser circuit drops suddenly with the first breath, whereas that in the systemic circuit gradually increases. The difference in pumping action that prevails in the normal adult exists essentially because of the difference in resistance to flow.

In the adult the resistance to flow in the pulmonary vascular bed is estimated to be only about one-eighth of that in the systemic circulation. On the other hand, it is estimated that a sizable amount of the mechanical energy, both pressure and kinetic, imparted to the blood by left ventricular ejection is still available at the point of venous inflow into the right ventricle, and is partly responsible for right ventricular filling and distention during diastole (*vis a tergo*). Connecting these two observations, one may wonder whether right ventricular contraction is necessary at all, or whether the left ventricle alone could not only circulate the blood through the systemic vascular bed but also through the pulmonary

vascular bed. The problem has been approached in different ways. It was first observed that major destruction of the right ventricular wall (by cauterization, for instance) causes but slight changes in systemic venous and arterial pressure [Bakos (5), Kagan (86)]. Yet a doubt remains, since some inner layers of the right ventricular wall are left intact in such experiments, and conceivably contractions of muscular bundles, which belong to the left ventricular wall, could still pull on passive strands of the remaining right ventricular wall and thus indirectly eject blood through the pulmonary ostium. In such a case, the noncontracting cauterized remainder of the right ventricular wall would passively compress the half-moon-shaped right ventricular cavity. Also, the still intact, powerful ventricular septum could contribute to the right ventricular systolic pressure rise. Acute experiments in which the entire heart is arrested and only the left ventricle, but not the right, is replaced by a mechanical pump, indicate that apparently stable circulatory conditions in both the systemic and the pulmonary vascular beds can be maintained using a single "left ventricle" pump [see also Rodbard & Wagner (137), Jamison *et al.* (85), Warden *et al.* (154), Patino *et al.* (127), Nuland *et al.* (121), Monod-Broca (115), Glenn (55)]. Obviously, the pressure in the vena cava is then raised to maintain sufficient pressure for the pulmonary circulation, and there may be an impairment to cerebral, coronary, and hepatic venous outflow. However, the conditions are compatible with survival of the animal. The question is not solely of academic interest, since it is not impossible to envision that some day surgical techniques will be devised to drain the entire systemic venous return directly into the pulmonary artery, thereby placing the entire load of circulation on the left ventricle.

THE PERICARDIUM

The function of the pericardium in the cardiac pumping process has been the subject of much debate. Some authors consider that the pericardium does not affect cardiac performance, because congenital absence of this structure in man is compatible with maintenance of a seemingly normal cardiac function [see Ellis *et al.* (43) and Hering *et al.* (74)]. Others have speculated that the primary function of the pericardium is to confine in space the pumping structures which are characterized by their expansi-

bility, pliability, and limited anchorage [see Pfulf, (129) and Nelemans (118)]. A number of additional functions have been ascribed to the pericardium, namely: protection of the entire heart from over-dilatation; protection from over-dilatation of the left ventricle only; protection from over-dilatation of the right ventricle only; increase of cardiac performance because of higher filling pressure; better harmonic coordination of right and left ventricular contractions; facilitation of atrial filling; and facilitation of the gliding of the epicardium through lymph lubrication.

Most experimental studies on the function of the pericardium concern abnormal situations such as are met in pericardial effusion and tamponade from various other causes [Feinberg (46), Adcock *et al.* (1), Evans *et al.* (44), Nerlich (119), Metcalfe *et al.* (112), Isaacs *et al.* (84), Bencini & Parola (9)]. The information from these studies, though in some respects limited to abnormal hemodynamic situations, has contributed much to the elucidation of normal functions of the pericardium.

Since some of the functions are implicit from the architecture of the pericardium, a brief anatomical-histological review will be helpful (118). The parietal pericardium, generally just called pericardium, forms a thin, but firm sac of connective tissue enveloping the ventricles and atria. At the base of the heart, near the entry of the veins into the atria, the parietal pericardium joins the visceral pericardium or "epicardium." Pericardium and epicardium are separated by a thin fluid film of pericardial liquor which is similar to the fluid filling the intrapleural space. The outer aspect of the pericardium is covered with a thin layer of loose connective tissue which constitutes the pericardial, or parietal, pleura. The pericardium is attached to the diaphragm with two septa (right and left) to the sternum and to the mediastinum. This anchorage limits the mobility of the sac and in turn confines the heart to a definite space within the thorax, especially in primates.

Histologically the pericardium consists of three layers of regularly oriented collagenous and elastic fibers, each oriented in a different direction. The fibers of the outer and middle layer form a thicker structure than those of the inner layer. In a preparation which is not submitted to stretch, the collagenous fibers appear wavy and the elastic fibers appear straight. Nelemans (118) showed that with an acute dilatation of the normal heart, the pericardium extends itself by approximately 20 per cent until the elastic fibers are markedly stretched and the

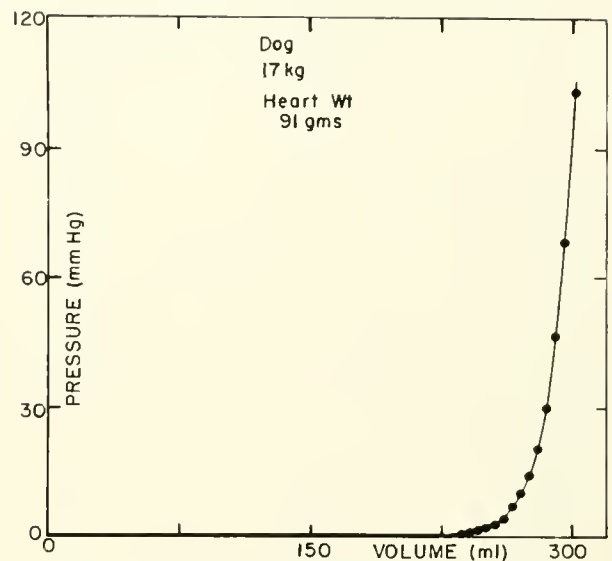


FIG. 25. Pericardial pressure-volume curve in a dead dog, determined after removal of heart. The volume of the heart is replaced by fluid injected into the pericardial space. [From Holt (78).]

rather tense collagenous fibers hinder further expansion. This elastic stretching is quickly reversible, since the sac will again fit snugly when cardiac dilatation is abrogated. If, however, the heart dilates beyond the limit of elastic stretch, which obviously can only happen if venous return and end-diastolic pressures rise substantially, then the pericardium will "give" or yield. However, this additional stretching is not quickly reversible and persists for a long time after the heart has returned to its normal shape, as evidenced by the slackness of the pericardial sac. The additional stretching is of "plastic" nature and can be attributed to the collagenous fibers which return only very slowly to their previous length after stretching. This dual mechanism of "elastic" and "plastic" stretch hinders acute overinflation (elastic limitation) but permits long term dilatation of the heart (plastic adaptation).

Nelemans' (118) views concerning the "plastic" behavior of the pericardium are supported by observations made in experimental pericardial effusion: following the infusion of 50 ml of saline into the pericardial sac in an open-chest dog, the mean intrapericardial pressure first rises markedly but then gradually decreases to a lower level. Withdrawal and immediate reinfusion of the same amount of fluid results in a lower pressure than the one initially obtained. Withdrawing the saline, but then waiting for about 2 hours before reinjecting it, results in

approximately the same pressure rise as initially recorded upon the first infusion.

The pressure-volume relationships of the pericardial sac without the heart were recently studied by Holt *et al.* (78) in experiments which emphasize the relatively nondistensible nature of the pericardium. The curve in figure 25 illustrates that, as the fluid volume in a dog's pericardial cavity increases, the pressure remains at zero until the volume has reached about 200 ml. Further volume increments cause a rather steep rise in pericardial pressure. The results of these and other experiments [Isaacs *et al.* (84), Berglund *et al.* (11)] point to an important function of the pericardium, i.e., to restrain the heart's cavities from overdistention.

In 1914, Henderson & Prince (71) showed that the filling-force relationships which later became known as Starling's law were such in the right and left ventricles as to prevent the engorgement or depletion of the lung blood. The lungs were further safeguarded against congestion by the fact that a sudden dilation of the left ventricle within the pericardium would prevent the filling of the right heart, limit the amount of blood that could be pumped into the lungs and thus prevent their engorgement.

There has been much debate as to whether during diastole the heart normally fills the entire pericardial sac [see also Wilson & Meek (162)]. Nelemans (118) concluded that the heart fills the pericardium completely during diastole and that the sac has a restraining influence upon the expansion of the heart. However, this question has not been studied extensively until modern recording techniques enabled Holt *et al.* (78) to follow the phasic changes of intracardiac and intrapericardial pressures during the cardiac cycle under various filling conditions ranging from hypovolemia to plethora. It was found that in an open-chest dog any increase in ventricular end-diastolic pressure above approximately 1 mm Hg causes a nearly equal rise in pericardial pressure. Since end-diastolic pressures of this order of magnitude are found under normal circulatory conditions, it appears that the ventricle does occupy the pericardial sac completely and even stretches it slightly at the end of the filling phase. Since under conditions of plethora a positive pressure is maintained in the pericardial space throughout the cardiac cycle, the transmural ventricular or transmural atrial pressure must then be taken as the difference between intracardiac and pericardial pressures rather than as the difference between intracardiac and intrapleural pressures.

In comparing the phasic changes in intra-atrial, intraventricular, and pericardial pressures, Holt *et al.* (78) also made observations which cast light on the contribution of the pericardium to the pumping action of the heart by facilitating atrial filling. The pericardial pressure drops markedly during the early part of ventricular systole. "Since the atria are located within the pericardial sac . . . , the pressure in the right atrium decreases in early systole and the atrium becomes distended by blood rushing into it from the great veins. A measure of the degree of this atrial 'filling pressure' is the difference between right atrial end diastolic pressure and the pericardial pressure in early systole." When the atrial pressure drops, "the pressure gradient from the great thoracic veins to the right atrium is markedly increased. This appears to be a mechanism by which blood is drawn into the atrium during ventricular systole, and in this way blood is ready to fill the ventricles immediately on cessation of ventricular systole. Thus, with the pericardium intact, the act of ventricular systole draws blood to the ventricle [sic] and insures ventricular filling in early diastole. These results are in agreement with those of Böhme and Brecher who showed that there was a large sudden flow of blood through the superior vena cava toward the heart during early ventricular systole. This has been attributed by several investigators, and most recently by Brecher, to the sudden piston-like downward movement of the atrioventricular junction attracting blood from the central veins into the right atrium. Our data indicate that the increased flow into the right atrium is caused by the sudden decrease in pericardial pressure with ventricular systolic ejection, and that this factor becomes greater with higher ventricular diastolic pressures. Confirmation of the importance of the pericardium in this connection is the observation of Brecher that the acceleration of venous flow toward the right atrium during ventricular systole is decreased by opening the pericardium. It would appear that the increased flow into the right atrium during ventricular systole was caused in large part by the decrease in pericardial pressure during early ventricular systole. The question as to how much of this flow is caused by a downward movement of the atrioventricular junction remains unanswered. Quantitative data on this point could be obtained by measuring the flow into the right atrium in the open-chest dog, with the pericardium intact and after complete removal of the pericardium" (78).

Obviously, both the piston-like downward move-

ment of the atrioventricular junction and the drop of pericardial pressure during early ventricular ejection are caused by the same force, i.e., the ventricular myocardial contraction. Which of the two factors is predominant in facilitating atrial filling during ventricular systole will not be easily decided.

From the presently available evidence one can conclude that the pericardium aids the pumping function of the heart. In contradiction to the widespread opinion that the absence of the pericardium does not have a noticeable effect upon the circulation, there is some experimental evidence that a large percentage of pericardiectomized animals develop heart hypertrophy and perform poorly on the treadmill [see Nelemans (118)]. It is quite possible that under conditions of rest or mild exercise the heart without pericardium can satisfy the metabolic demands of the tissues. However, under conditions of strenuous exercise the reserve power of the heart without pericardium is probably diminished.

CLOSING REMARKS

In recent years the opinion has been often voiced that hemodynamics is a dead science, in which no more essential work needs to be done. This view refers primarily to the mechanical features of the cardiovascular system which are supposedly well known. It applies less to the regulatory aspects which admittedly require further clarification. However, the analysis of such a presumably simple function as the heart's normal pumping, even without consideration of any neural or hormonal regulatory processes, reveals wide gaps in our knowledge.

There are numerous reasons for these shortcomings.

Many of the measurements on which present concepts are based were obtained under highly artificial conditions, such as excised heart preparations and open-chest animals, which limit the applicability of the results to intact normal organisms. Findings in one animal species often cannot be transferred or extrapolated to other species. For instance, the mechanics of cardiac pumping in man differ from those in other animals because of his upright position, minimal splanchnic pooling, and several other factors. Finally, measurements are often performed with inadequate instrumentation. For example, errors caused by insufficient sensitivity and time resolution make it difficult to correlate simultaneous events in the cardiac cycle.

Only rather guarded conclusions can therefore be drawn from the available experimental evidence as to the exact nature of the heart's pumping function. Wide discrepancies of information obtained with different methods need to be reconciled. For example, measurements of the ventricular volumes by various methods differ so greatly in their order of magnitude that it is today still impossible to state how large is the normal functional residual capacity of the heart. Obviously, views based on insufficient data must remain in the realms of speculations and postulates. This is the state of knowledge about many age-old problems such as cardiac filling and the precise moment of valve closure. How much more complex these problems become under various pathological conditions does not need to be elaborated upon. In view of the recent progress in the biomedical sciences, it is shocking to observe how a seemingly simple mechanical process such as cardiac pumping still remains so enigmatic.

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The physiology of the aorta and major arteries¹

JOHN W. REMINGTON *Department of Physiology, Medical College of Georgia, Augusta, Georgia*

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AT OUTSET, may I say that this article on the function of the aorta and the major arteries makes no pretense of being an authoritative review of the literature, and is not only a generalized treatment but is written with a bias. I came to cardiovascular study via Biology, in an era when Physics was not such a firmly trothed bride of Physiology. I do not think glibly in terms of abstract formulas, of electrical analogues, or the other erudite devices now so commonly used to clarify the complex problems which underlie pressure wave formation and propagation. I believe that I understand a process only when I can construct some

sort of a visual image of just how it operates. In many aspects of the subject such a visual model is at present impossible. I can only describe what I have been able to gather about the function of the major arteries, and speculate about what trends future research will follow.

These large arteries serve two clear functions. First, they comprise a network of conduits through which blood is moved from the centrally located cardiac pump to the various capillary beds. It is important that this transfer be made with a minimal loss of energy. The problem of proper conduit design became more acute when the body form became elongated, instead of remaining spherical. Second, the distensible wall of the vessels allows a temporary storage of blood during the ejection phase of the pump cycle, which allows a buffering of the oscillatory pressure changes. This aspect will be spoken of as the reservoir action of the vessels, admittedly an inadequate label. While the buffering action might serve to protect the small vessels from large pressure changes, it also involves considerable change in the conduit properties.

We cannot yet form a definitive analysis of the effectiveness of aortic design in meeting these fundamental requisites. Progress has been handicapped because it has been so difficult to make critical studies on intact vessels. Pressure changes at various points along the arterial system have been measured often over the past 50 years (1, 16, 18, 28-30, 40, 42, 99, 116, 132, 134, 135). This has given us knowledge, still far from complete, about the speed of pulse-wave propagation, the contour of the pressure pulse as formed in the upper aorta, and the changes in this form as the pulse moves into the distal aorta and large arteries. It is doubtful that any great progress toward an understanding of arterial dynamics will be made by

¹ This manuscript was completed January 15, 1961, and its references include only papers I had read in published form at that time.

further studies on pressure values alone, without a simultaneous recording of vessel diameter or flow.

A study of two parameters has often been attempted, but not too successfully. It has not proven practical to remove the aorta from the body and insert it into an artificial system where the volume change and the flow through might be measured directly, as from a calibrated stroke of a pump. The problems of coupling this distensible tube to rigid fittings without having an orifice that will severely distort the flow pattern are considerable. No effective means has been devised to occlude completely all exit vessels, including the vasa vasorum, and thus prevent loss of fluid along the length of the vessel. Sometimes a rubber insert has been used (137) but, since most rubber tubes are less extensible than the aorta, this stratagem may have confused matters more than it helped. And we still have no pump which has an ejection pattern like that of the ventricle. Curiously enough, an artificial pump capable of producing a pressure rise similar to that seen with a natural pulse invariably produces turbulence and vibrations of the pressure recorder sufficient to obscure the pulse contour being formed.

A recording of aortic flow *in vivo* by a technique which requires vessel cannulation causes enough distortion of the pressure pulse contours that one must be cautious in inferring a direct pertinence to the intact system. Fortunately, several techniques are now in use for the recording of flow (27, 31, 55, 82, 110, 120, 131) and the registration of diameter change (88, 91, 113) which do not require cutting the vessel. Most flow recorders do require a crimping of the vessel in the region where flow is being measured, which may not be without effect on the flow profile. As yet, the frequency of many such devices usually does not approach that of a good pressure recording system, so that they may not be able to give a faithful picture of rapid change.

An engineer faced with the problem of designing a conduit system for the most efficient movement of blood would start with some basic equations. First, there would be the Poiseuille formula which states that the pressure fall (for frictional energy dissipation) will be directly related to the flow rate, the fluid viscosity, and the length of pipe, and inversely related to the fourth power of the radius. The last is because adsorptive forces between the fluid and the wall prevent or retard longitudinal movement of the outermost fluid layer. This in turn forces the adjacent shell to shear past it, retarding it with a frictional dissipation of energy, which in turn slows the next shell of fluid, and

so on to the middle of the pipe. For a given volume flow, the greater the pipe diameter, the less is the total fluid frictional loss. He would also include in his formulas factors relating to the smoothness of the wall and the material of which his conduit will be made, since these condition the size of the boundary layer. He must make corrections if the fluid does not have a constant viscosity at all flow rates, as blood apparently does not (9, 86). He also knows that an equation which applies to laminar flow will not be correct if fluid molecules whorl laterally across the fluid shells, i.e., when the flow becomes turbulent. The frictional cost increases whenever this happens. Finally, when he is required to use pipes of different sizes, he must carefully design the transition areas so that turbulent eddies will not form. Tapered changes in diameter are less conducive to turbulence than abrupt shoulder joints.

All these formulas, which may be found in texts on hydraulics, are based on the assumption that flow is being maintained steady, and that the conduits have rigid walls. But blood flow is not steady, for it shows several accelerations and decelerations with each pump stroke. A calculation of the energy loss accompanying such rapid changes in flow rate must be complicated. A whole new set of equations will be required and, to check them, we must be able to measure precisely the amount of acceleration in all parts of the arterial system. Quantitative evaluations of the degree of smoothness or of the absorptive forces for plasma on the endothelial lining cannot be given. Microscopic observation of moving blood in tiny vessels has shown that the red cells congregate in the center of the stream, which is presumptive evidence for a greater axial velocity. Whether we can assume from this that a parabolic flow distribution would be found in the large arterial vessels is open to question. While streamline flow has been described for the aorta (92), there remains some question as to whether a normal flow pattern could be said to have persisted during the measurements, and whether the streaming would apply over the whole cardiac cycle (84).

The large arteries are not rigid, so that any equation relating energy dissipation to tube radius will be complex. Further, the arterial system seldom has any tubes which continue uninterrupted for an appreciable distance. Each vessel has frequent branchings. With the exception of the ascending aorta (44) and the main pulmonary artery (88), with each branching there is an increase in the aggregate cross-sectional area. These junctions appear smooth and tapered, so that the orifice problem is probably at its simplest.

Further, most trunk vessels show a gradual taper through their length. Exceptions to this, that come to mind, are a region of the descending thoracic aorta and one of the carotid artery, which appear to be more nearly true cylinders.

Too detailed a particularization of the various factors which give rise to frictional resistance may be nonessential. The total effect of them all should be measurable by a decrease in mean pressure, over a whole cardiac cycle, from the upper aorta to the peripheral arteries. Several studies have shown that in the aorta such a decrease is so small as to be within the error of measurement (42, 68). In fact, there is no clear loss in mean pressure in man until the brachial or femoral arteries are reached.

Despite this small frictional dissipation of energy attending propagation, there is a very clear difference between the pressure energy developed in systole and in diastole. Except under rare circumstances, the mean systolic pressure is greater than the mean diastolic pressure. This excess of pressure energy could denote an inability of the stretch of the extensible wall to keep pace with the force applied by cardiac ejection, so that energy is stored in potential form in the visco-elastic walls, or it could indicate a different pressure-flow relationship in the large vessels being filled during systole, and that which marks "drainage" through the peripheral arterioles.

To go from generalities to the specifics, an analysis of aortic function could be focused upon three large questions: 1) What are the essential features of the tension-length curves shown by the walls and the derived pressure-volume curves, and to what extent are these curves subject to physiological and pathological change? 2) How does wall distention affect the conduit properties of the vessels? 3) What factors influence the capacity of the arteries to serve as a blood reservoir?

MEASUREMENT OF AORTIC DISTENSIBILITY

General Characteristics of the Tension-Length Curve

Until quite recently, measurements of the extensibility of blood vessels were made on isolated tissues, using two procedures (11, 15, 22, 37, 51, 62, 65-67, 76, 107, 118). Usually a ring (for circular stretching to produce an increase in circumference) or a cut strip (for measuring longitudinal change) was subjected to weight loads, the changes in length being recorded. In a few cases, volume was injected into a

tied-off vessel, recording pressure. Any change in the other dimension, e.g., a longitudinal change during circular stretching, was either inadequately measured or ignored. Although the specific techniques for increasing load have varied, the stretches were made rather slowly so that the vessel could approach, if not attain, a stable length value, i.e., a "static" value. Whether the load was applied in a continuously increasing manner or stepwise, the data were generally presented as a single tension-length curve covering the whole physiological range. All workers agree that such a curve is not linear, but shows a relatively great extensibility at low tension settings and a progressive wall stiffening as the load increases (fig. 1). This curve is therefore different from that shown by metals, even those that obey Hooke's law over the greatest part of their extension, or by rubber, where the length change becomes relatively greater at high tension levels (46). A rubber tube wrapped with a fibrous jacket, such as a garden hose, shows the same type of curve as does the aorta (14). Rings taken from the aorta or from arteries appear to differ only quantitatively. Further, the longitudinal stretch curves are qualitatively similar to those obtained with a circular stretch.

The tension given in figure 1A is the weight load divided by the product of the length of the ring of the thoracic aorta and the wall thickness. This can be converted to internal pressure by dividing by the radius. To express pressure in the usual physiological terms of mm Hg, the obtained value is divided by 13.5. We can calculate the volume per unit length of vessel as πr^2 . Both pressure-diameter and pressure-volume curves show two inflections, to give the curve a somewhat sigmoid appearance (figs. 1B and C). The pressure level at which these inflections are seen varies with different regions of the aorta. Hence both inflections are set at a higher pressure in the upper aorta than in the lower, and the lower inflection may not be seen at all in the arteries (46). There is no simple formula which will fit this sigmoid type of curve, or even that portion of greatest physiological significance. At outset, it is clear that any comparison of vessel distensibility from time to time, or between animals, will require the use of the same arterial region and the same pressure span.

There are several inadequately explained properties of the isolated specimens which seriously affect the recorded extensibility curves. First, as the vessel is dissected out of the body, there is an immediate shortening of its length and a tensing of its walls. This is true whether the animal has just been killed,

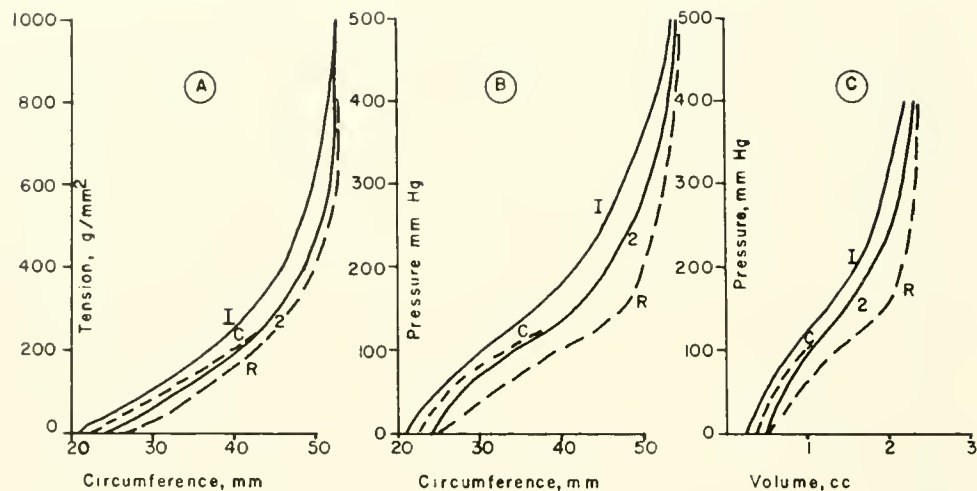


FIG. 1. Stretch curves for a ring of thoracic aorta of a dog. In situ length = 10.5 mm. Curves 1 represent the first stretch curve, made by continuous tension increase over 1 min. Curves 2 are the results of a second stretch identical in load and timing to the first. Curves *R* show the curves taken during the gradual release of tension, over 1 min. Curves *C* show the effect of muscle contraction by immersion of the ring in epinephrine.

or has been dead for some time, and whether the voluntary muscles are in a state of rigor mortis or not. The change develops no matter how carefully the removal is done. The interpretation placed upon this change in the past is that it reflects a strong contraction of the smooth muscle contained in the wall. Aside from the speed of its development, which contrasts with the slower time course of muscle contraction, and the lack of correlation between the amount of longitudinal shortening and the proportionate amount of muscle in the wall (ascending aorta, for example, contracts to the greatest degree), there are other features which do not fit too well with this interpretation.

When such a tensed ring is subjected to stretch, and the load is then removed, the walls are no longer so tense, and the circumference is about 30 per cent greater than before the stretch. What was not realized in the earlier studies was that the amount of this diameter increase bears a direct relation to the total stretch imposed (96). Now, if a second stretch of the same size is made, the stretch curve starts from the greater initial value and courses almost parallel to the first through the region of greatest extensibility (fig. 1A). Then, as the wall stiffens, the second curve becomes enough steeper that it merges with the first some time before the peak load is reached. This merging argues against a conclusion that the first stretch had caused some irreparable tissue damage, such as an internal tearing. If, after the first stretch and stretch release is completed, the tissue is allowed

to remain unloaded for a long period (several hours), the original small diameter may be almost, if not fully, restored. If the first stretch had "pulled out" an existing muscle spasm, why should it reform and take so long in doing so? Experiments designed to test this "pulling out" idea with smooth muscle organs, such as the gut, have given little indication that an active contraction itself is eliminated by an extension of the whole tissue under load (6, 101).

With a relatively large load, a third stretch made after the second usually gives a stretch curve identical to that of the second. This fact has been recognized by many past workers who were aware that a large initial stretch, which was not quantitated, made subsequent stretch curves more reproducible. Such reproducibility does not mean that they are necessarily more descriptive of the behavior of the vessel in vivo. With a similar load, successive stretches may start from progressively increasing initial diameters, but a reproducible stretch curve is reached within 5 to 10 stretches. Unfortunately, when examining past studies, it is impossible to be sure whether a preliminary stretch was used, and, if so, how much tension was involved and how long a time interval was allowed before the recorded stretch was made.

The Hysteresis Loop

Until recently, too, little attention was paid to the fact that as the loads were removed the length curve did not follow, during this stretch release, the previous

stretch curve (fig. 1). Hence for any given stretch two different tension-length curves must be considered, one for the extension and the other for the elastic recoil. The difference between the two comprises a hysteresis loop. The amount of hysteresis is always greatest with the first stretch done after a prolonged rest period. If this first stretch is followed by repetitive stretches of the same size, the hysteresis is progressively reduced until it becomes relatively constant. The number of successive stretches required to achieve this stable loop varies among vessels, for two or three stretches will suffice with the aorta, but more may be needed with a muscular artery. In the gradual reduction of hysteresis, the stretch-release curve remains almost or completely constant, its values being set by the peak load used (96). It is the extension curve which shows progressively larger length values at any given tension value. Hysteresis is present in some metals, too, although its amount is relatively small as compared to that seen with vascular tissues.

The presence of hysteresis is often taken to indicate simply a viscous retardation of the extension of elastic elements, and handled in formulas as though it were simple viscosity (48). This would mean that the size of the loop is an index to the frictional energy dissipation, which, in turn, would be directly related to the rate of the imposed stretch. Hysteresis of the vessel wall is not so easily formulated. We can summarize its main features by saying that at least three factors seem involved.

1) While a viscous retardation is present, it can be demonstrated for the aorta only at very rapid rates of stretch (96). A rate dependency has not been seen for the stretch-release curve. The muscular arteries have more rate-dependent hysteresis than does the aorta.

2) When a stretched length is held constant for a period of time, some internal elongation of elements still continues, so that the tension falls. This decline is called stress relaxation. Or if a tension value is maintained, the length will continue to increase slowly, which process is known as "creep." The amount of creep is a function of time, but the relation is not easily formulated in quantitative terms.

Muscle physiologists have frequently referred to this slow continued elongation under stress as plasticity (13, 93). This use of the term "plastic" is not very appropriate. With metals, when an applied increasing stress reaches a certain critical value, the material becomes deformed. The length change accompanying this deformation may show the properties of viscosity, but the term plastic does not denote the presence or

absence of such viscosity. Once deformed, the material does not return to the original length upon removal of the stress, but retains the increased length. The choice of the word plasticity for the slow elongation of muscle lay with the belief that any reversibility could be brought about only by an active muscle contraction. However, the process which underlies stress relaxation is spontaneously and completely reversible, if enough time is allowed, whether the muscle is alive or dead (101). Muscle contraction may, of course, hasten the return to the original length. Stress relaxation involves a complicated type of internal viscosity which is so arranged that the driving force for length return lies with some parallel elastic unit which is under stretch.

Just as with rate-dependent viscosity, the stress-relaxation component is but a minor part of hysteresis as seen in the aorta (96). Its influence is more evident the longer the vessel is kept at a peak load, or the longer the vessel remains under no load, so that creep recovery, or the reversible phase of stress relaxation, can continue.

3) When, with successive stretches, a final "stable hysteresis loop" is obtained, neither the values from the stretch phase nor those from the release phase show any dependency upon the rate of stretch, and a dependence upon time cannot be easily described. For want of a better term for the remaining factor, which seems to dictate the greatest part of the hysteresis behavior, I have called it simply an architectural rearrangement. The change is certainly dependent upon the amount of stress and involves a reversible change in length. While there must be some time dimension to this internal rearrangement, the change presumably is very rapid. It may be at a molecular level or at a tissue fiber level.

What should be firmly emphasized is that a tissue probably has a great many different viscous elements with different time constants. When we refer to such a tissue as being visco-elastic, it does not mean that all the different viscosities can be lumped to give a single viscosity, with an easily definable rate dependency.

In view of the complexities that influence a tension-length curve, it is possible that we should think of the firming of the aortic wall, upon removal from the body, in terms quite different from that of a muscle contraction. The vessel is held in situ under considerable longitudinal restraint (104, 107). When a segment is cut, elastic elements held lengthwise under stretch should recoil and make the wall thicker. When, with a circular stretch, no attempt is made to restore

the original length, there could be a reorientation of these elements into the circular plane, leaving a ring with a larger circumference. This indicates, as is probable, that both longitudinal and circular elastic elements are part of a linked network, and therefore not independent. In our studies on isolated rings, when we converted the actual tension-length values to pressures and volume, we used *in situ* length rather than the actual one. This mathematical step was better than using the actual lengths, but is not necessarily sufficient as a correction if elements previously oriented longitudinally were participating in the circular stretch.

This is not to say that all the hysteresis phenomenon could be due to a progressive recruitment of longitudinal fibers into a circular plane. The loop still present, despite many consecutive stretchings, probably denotes a structural rearrangement of elements under load that were already in the plane of the stretch. It is admittedly strange that such a rearrangement would have no clear time dimension.

An occluded, *in situ* aorta being pulsed by volume injections shows a similar pattern of hysteresis and change in extensibility curve with successive stretches (5). We attempted a quantitative assessment of possible differences between total aortic distensibility, as measured by injections of saline into dead but *in situ* aortas, and as compiled from stretch data made on rings cut serially from the same vessels (103). The volume required to produce a given rise in pressure was greater than that estimated from the first stretch curves of the isolated rings. It was also a little greater, although perhaps not significantly so, than that expected from the second stretch curves.

On hindsight, this comparison may not have been so definitive as we supposed. At the time the experiments were done, we were not so aware of the large effect of the time interval between successive stretches, of the initial pressure level, and of the peak pressure reached, on the contour and values of the extension curve.

Selection of Representative Curves

Historically, an interpretation of vessel wall architecture has been based on the contour of a first, or a second, large and continuous extension curve. It should now be obvious that this contour should not be regarded as characteristic of wall extension during unceasing, repetitive stretches, such as would be present during life. How large the differences between the two curves might be will be elaborated more

fully later in this paper. Ultimately, a study of vessel wall behavior must be based on pressure and diameter or volume measurements made during life. Such studies will be technically difficult, and interpretation of the records will be difficult, since in life the heart rate and the pulse pressure are continually changing from beat to beat. Work on this problem is in progress in a number of laboratories, and some results have been published (87, 91, 113). Unfortunately, these show some differences, and the adequacy of the various techniques has yet to be firmly established. But taking the data as they now stand, it appears possible that while the amount of hysteresis varies among arteries, it is probably less than that shown by the isolated rings. This may be because the living aorta is being cyclically stretched without pause.

The suggestion, which needs further corroboration, that the diameter change of a living vessel for a given pulse pressure is less than that given by an isolated ring (61, 78, 87, 91) could indicate that, for some quite unknown reason, a very different distensibility is present in the living vessel. In one study (91) the reported diameter change is so much smaller that our whole concept of the functional character of the vessel, as will be developed in this paper, would have to be changed. We are not satisfied yet that the instrument used could record a change as large as that expected from the ring stretch data. Reconciliation between the various sets of data should not be long delayed.

Until the properties of the *in vivo* aorta are known more surely, we must base a description of the factors which might condition the extensibility curve on data taken from isolated rings. If these data should eventually prove quantitatively wrong, we can only hope that the fundamental properties of the vessel would nonetheless be qualitatively the same. First, the nonlinearity of the continuous stretch curve is evidence for an internal architecture more complicated than that seen even with rubber or other polymers. In the range of maximal extensibility, the aorta shows more length change per unit tension increase than any other material of comparable wall thickness. Nature seems to have created a far better volume reservoir than man can duplicate.

Histological Considerations

We know from histological evidence that the large vessels have four general types of tissue—endothelial cells (with associated intracellular materials), smooth muscle cells, elastic fibers, and collagenous fibers. Because histology texts tend to emphasize a collection

of these tissues into more or less well-demarcated layers, physiologists have taken what probably is an oversimplified approach to an analysis of wall extensibility, and have considered each of these tissue types to be unconnected and arranged in parallel. But while elastic tissue does appear to be condensed into layers, it also is interspersed between muscle and collagenous fibers. And there seem to be connections between the gross layers themselves, which means that we can hardly consider the influence of any one tissue type alone. Nor are we at all certain about the elastic characteristics of the different tissues, even if they were to behave independently. The extensibility of the endothelial cells is relatively unknown in any quantitative sense. Since they comprise but a very small part of the wall, and since they certainly are not stiff enough that they are torn by even large stretches, they probably are relatively extensible, and their influence can probably be neglected for the present. An estimate of the extensibility of collagenous fibers has been taken from that shown by tendon, although the collagenous fibers of the latter are larger and more densely packed. As opposed to a tissue containing elastic fibers, tendon is quite inextensible and shows a linear stress-strain relation with no discernible visco-elastic properties (21, 52, 67, 97, 103, 112). The aortic wall stiffening seen when the pressure rises above about 100 mm Hg has thus been attributed to the resistance to stretch offered by the enclosing jacket of collagenous fibers (21, 103). Aortic walls from which elastic tissue and muscle have been digested show a similar stiff wall (50, 111). This jacket must fit loosely and be considered in parallel to the underlying elastic tissue. Once it starts to participate in the stretch, it will assume the bulk of the applied load.

On the basis of stretch curves shown by ligamentum nuchae, which is predominantly elastic tissue, elastic fibers are much more extensible than collagenous fibers. Chemically treated aortas which retain only their elastin show an increased extensibility, one not greatly different from that of the whole vessel in the lower stretch range (51, 52, 74, 111). Most workers ascribe a linear stress-strain relation to these fibers, too. Hence my work (97) seems to stand alone in the claim that ligamentum nuchae shows a nonlinear curve not unlike that of the arteries (with a stiffening in the upper tension range despite the absence of any clear collagenous fibrous coat), and also has visco-elastic properties similar to those of the aorta. Since the elastic fibers in both organs seem arranged in a reticulum, and since the visco-elastic properties of

dog ligamentum nuchae seem clear, the following analysis will be based on a similarity in stretch behavior of the two tissues.

Assessment of the extensibility of smooth muscle cells is on most insecure ground. Studies have been made of the stretch properties of muscular organs, such as the bladder or gut, for this purpose (6, 97, 101, 102), although the muscle fibers here are enmeshed in a loose weave of collagenous and even some elastic fibers too. If this muscular tissue is subjected to a moderately rapid stretch, its extensibility is only about a third as great as that shown by ligamentum nuchae (97). But because these tissues have such a pronounced time-dependent creep, if one waits for the length to approach a final value under a given load, the total extensibility is greater than that of elastic tissue. This has been the procedure used when elastic moduli for muscular structures have been derived. But it seems unreasonable that the muscle contained in the aortic wall could show such a prolonged creep. If the muscle cells are coupled to the elastic fibers, creep would be effectively prevented by the resistance these fibers would offer to an elongation. Of course, the greater the amount of muscle involved in the vessel wall, the greater would be the creep. At one extreme, the umbilical artery, which is almost solely muscle, shows a very pronounced stress relaxation under load (122, 141). In most large arterial vessels the relaxation is of more limited degree. Hence the muscle contained would probably be stiffer than the elastic fibers, which would remain the most extensible part of the wall.

It should be noted that the pulmonary artery shows a difference in distensibility behavior from the aorta. The form of the stretch curve is more akin to that of a large vein (105). The vessel shows more creep than does the aorta (32). The form and the total length change of the stretch curve are different in pulmonary vessels that have been frozen and thawed than when simply kept in Ringer-Tyrode solution (a reflection of the effect of viable muscle?) (32).

There is histological evidence that, in the aortic wall at least, muscle cells, elastic fibers, and some collagenous fibers are interlinked into a three-dimensional network (11, 109). The elements in this network could be partly in series and partly in parallel. The extensibility of the whole tissue could be a reflection of the form of the net just as well as it could be conditioned by the individual tissues. For example, Bull (20) showed that while a single nylon thread obeyed Hooke's law, and had no visco-elastic behavior, a stocking woven from such a thread

showed a bowed extensibility curve not unlike that of the aorta or of ligamentum nuchae, and also showed a pronounced hysteresis loop. When I stretched a stocking by the techniques used for an isolated ring of aorta, the dry specimen showed an appreciable rate-dependent element (viscosity) in the tension response to a given strain. When the stocking was wet, this viscous element was relatively reduced, and there was unmasked both a prolonged creep and the "architectural dependency" which is so conspicuous for the hysteresis behavior of the aorta.

If the analogy of the stocking is valid, the first part of the stretch curve of the aorta would reflect only a geometrical rearrangement of the net. The resistance to stretch would be a function of the looseness of the "weave" and the presence of a lubricant (as in the wet stocking); there also could be a "set" of the net, which could be subject to change with time, with muscular activity, and, very definitely, be influenced by the size of a previous stretch. When, under applied load, the net lost its form, the extensibility would progressively decrease, both because the mechanical advantage of the fibers in resisting the stretch would be increased and because the fibers themselves would now be involved in the extension. If our ideas of the relative extensibilities of the different components is correct, and if they were arranged in the net in series, the elastic fibers, being most extensible, would condition the extension of the whole wall. With more load, these elastic fibers would become stiffer (as they do in ligamentum nuchae), and other components of the net could be increasingly involved. Probably the idea of a parallel outer collagenous jacket should still be retained to contribute to the final wall stiffness.

In an earlier analysis (103) we treated the aorta as though it contained the three tissue types as arranged in parallel. Since muscle had to be able to reduce the vessel diameter below its normal unloaded size, we conceived of the elastic jacket as fitting loosely over the muscle coat. This would mean that muscle alone would be involved in the very first part of the stretch curve, and that only later in the stretch would the elastic fibers start to participate. Such an arrangement seemed amply supported by evidence obtained with stretchings repeated daily, using rings as they were allowed to putrefy. In this process muscle cells lost their integrity first and the unloaded diameter increased while the initial slope of the stretch curve became steeper. Much later, the elastic fibers softened and their continuity became disrupted. Now the unloaded diameter had again increased, and the aorta

showed a stiffness not unlike that seen at high load levels in the normal state, which was attributed to the collagenous fibers still present. The net model would fit these putrefaction studies equally well, for loss of muscle could partly disrupt the net to give an increase in unloaded diameter and, at the same time, leave the wall less extensible.

There still remain several features of the viscoelastic behavior of the aortic wall which would not be easily explained on the basis of the net. And the details of net construction are left purposefully vague. The general concept has much in common with the model proposed by Burton (21), except for its de-emphasis of the specific location and role of the muscle fibers themselves. He was much concerned that the muscle be afforded a great mechanical advantage, so that it could always effect a diameter change. Hence he placed these fibers across the plane of a fibrous net, which would protect them from elongation. In muscular tissues it remains uncertain that the contractile ability of muscle fibers is necessarily impaired when they are elongated, even by the amount that may normally be developed in an organ such as the urinary bladder. Further, it may be that even in smooth muscle organs the muscle cells are arranged into a somewhat similar net (101, 102). It may be that the muscles in the aortic wall are attached to adjacent loops of the net (which would give them more of a parallel arrangement than a series one with the elastic and collagenous fibers), so that they could, by shortening, act to "open the weave," and perhaps increase its "set." This need not mean that the stiffer muscle would now condition the extensibility curve, for we could have, with extension, a warping of the net toward these muscle links. Hence, the internal architecture could be quite different when muscle was contracted than when relaxed, even though the diameter values under a given load might be the same.

Effects of Active Muscular Contraction on Distensibility

Whether it is necessary that a model provide muscle with a large mechanical advantage cannot be answered. We are not sure just how effective muscle contraction really is in a vessel under a load equivalent to that of the usual physiological pressure values. Much work is currently being done in which strips of aorta are used as conveniently long tissues to test the effect of drugs, or changed electrolyte environment, on muscle contraction (35, 79, 80, 121). To be useful as a bio-assay material, such strips must be

under minimal load. Isolated aortic rings will, when unloaded, respond to immersion in epinephrine, for example, by a shortening of both their diameter and length, to produce a pressure rise of some 3 to 5 mm Hg. But if these contracted rings are subjected to stretch, the decreased diameter is lost rather early (fig. 1A), so that by the time loads equivalent to the usual working pressures are reached, the contracted and relaxed rings show identical extensibility curves. With stretch release, the diameter does not return to the contracted size. Either the muscle loses its contraction early in the stretch, or the other parts of the net have contributed more than usual to the total extension. Even in muscular organs, such as the bladder (102), the effect of contraction on the extensibility curve is small, and the contraction itself seems not to be eliminated by the imposed stretch (97, 118). The extensibility of a muscular organ is not very different in the contracted or relaxed state (6, 13).

What is more disquieting is that if an aortic ring is first subjected to a load equivalent to a pressure in the usual physiological range, immersion in epinephrine will no longer produce a discernible diameter or pressure change. It is hard to accept this finding as rational. Yet neither viable isolated specimens nor a temporarily occluded aorta *in situ* (5) has been shown to have a more powerful muscle action. This is not to say that a contraction in muscular arteries, where the ratio of wall muscle to internal diameter is greater, could not influence the diameter at the higher pressure levels.

Attempts have been made to record the effects of muscle contraction in the intact aorta while it is being pulsed by the heart. Most of these I have learned of through conversations, since there is reluctance toward publication of negative findings. In the literature are the older experiments of Wiggers & Wegria (138) in which an aortograph was placed around the thoracic aorta of a dog. After an intravenous injection of epinephrine or elicitation of a strong pressor reflex, there was a recorded decrease in diameter (the actual values not being given) at a time when the aortic pressure was not changing. For many years these results stood unchallenged and yet unsupported. More recently, Patel and co-workers (88) found a change in both diameter and wall stiffness in the main pulmonary artery with muscle contraction, a change persisting through several normal pulsations. The pulmonary pressure is, of course, much lower than that of the aorta and the wall architecture is not the same. Then Peterson and

co-workers (91) showed a change in diameter and an increased stiffness, with arterial pressure unaltered, when the femoral artery or carotid artery was painted with norepinephrine. Opposite results were obtained with acetylcholine. The authors claim a similar directional change, but furnish no supporting figures, for the aorta. These results, and particularly the claim for the aorta, must be amplified and confirmed.

Diameter and extensibility changes in the aorta of living animals following the use of constrictor or dilator drugs have been recorded (78) which do not appear to fit with the stretch data obtained with isolated rings. Since the arterial pressure also changed, and since the physiological distensibility curve for the intact aorta, quite aside from any muscle action, remains to be formulated, an attempt to interpret these changes on the basis of muscle contraction would be premature.

We are not yet in a position, then, to answer the long-debated question as to whether muscle contraction should increase or decrease the wall extensibility. The effects of such contraction on the stretch curves shown by isolated vessels are difficult to phrase in terms of generalities. With an unloaded vessel, contraction is not followed by relaxation. Instead, over a period of time, the wall gradually becomes stiffer, as though the fibers had been reset to the shorter length. Whether the contraction had any essential role in this resetting, aside from the first reduction in length, remains uncertain. Depending upon the amount of this resetting, a small stretch, starting from zero tension, will reflect this initial stiffness of the wall. With more stretch, the distensibility suddenly increases, so that the stretch curves of the once contracted and the relaxed ring are now parallel. At higher loads the two curves merge. If one assays distensibility, it must always be with respect to the amount of load used. Thus, if the stretch is sufficient to cause the shift toward the increased distensibility, one would conclude that the muscle contraction had rendered the wall more extensible. If the assay were on the basis of the very first part of the stretch curve only, one would reach the opposite conclusion of a lessened extensibility. Whether the effects shown by an unloaded tissue have any pertinence to what might happen at physiological pressure levels remains to be shown. If, for some reason, the muscle in the living aorta were more powerful, or if the imposed stretch were made quite small, we might anticipate a decreased wall distensibility. Even so, any interpretation of the effect of muscle contraction would have to be phrased in

terms of the shape of the stretch curve, and the total stretch employed.

Effects of Aging on Arterial Distensibility

The effects of aging on arterial distensibility are supposed to be well established—at least the textbooks so report. The actual evidence leaves much to be desired. On the one hand is the story of pathologists that aging is accompanied by a reduction in muscle mass and in elastic tissue, with a replacement by collagenous fibers. The reduction of muscle mass needs documentation by actual cell counts. Chemical digestion of the aortic walls, to leave only elastin, left Lansing (74) unwilling to accept the dictum that the elastic fibers had been reduced in number with age. He would, of course, accept the possibility of a chemical change which might influence the wall extensibility.

Extensibility studies made on isolated vessels taken from humans of different ages suffer from our uncertainty about how to compare extensibility among different specimens. The repeatedly quoted studies of Hallock & Benson (37), based on a small series, in which only the average results of a given age group were presented, showed some decrease in extensibility with age, with the only truly large change seen in individuals over 70 years. The comparative data were expressed in terms of an elastic modulus ($\Delta P/(\Delta l/l)$). Here, as in all other reports (10, 62, 66, 81, 107, 127), there was a progressive increase in unloaded diameter with age, which in itself could increase the value of this modulus. In a study of a larger series of human aortas (107) we presented results taken from the second of two consecutive stretch curves. Variations within the age groups were large. While the group averages showed a progressive increase in initial diameter, it was also true that a man of 68 showed the same diameter as a girl of 18. All these aortas were screened so as to include none showing atherosclerosis, and any from individuals with a history of hypertension were placed in a separate category. The diameter increase was especially noticeable in these hypertensives. The slopes ($\Delta P/\Delta l$) given by the stretch curves also showed intraindividual variation, but they were very much more constant than were the initial diameters, and there was no clear trend for this slope to change with age. A changed modulus value with aging was, then, predominantly conditioned by a change in the initial diameter.

Expression of Extensibility in Terms of Moduli

This raises the question as to just how meaningful a modulus value is in expressing extensibility data. Certainly having to present a whole stretch curve for each specimen studied is cumbersome, and such data are difficult to handle statistically. But a modulus is supposed to afford insight into the architecture of the specimen. Thus when a physicist wishes to describe the extensibility as a property of a material, he uses Young's modulus, or a related one, which is simply the ratio of the applied extending force or stress, as expressed per unit area of material, to the proportionate change in length from the unloaded value. Most of his materials are so stiff that the strain is small. Further, the material promptly returns to the initial length upon removal of the stress, and in measuring extensibility he obtains a clue to the force of this return. He therefore calls his modulus one of elasticity, despite the fact that he is measuring extensibility and not elasticity at all. Any time delay in effecting the strain is usually so brief as to be inconsequential. When the ratio of stress to proportional strain is constant (he carefully avoids a load sufficient to cause permanent yield or plastic deformation), this ratio can be calculated by using any convenient load. Because most materials do not have a constant ratio, and some, as cast iron, depart quite significantly from a linear relation, he tries to make his applied stress as small as feasible.

When we turn to materials such as the polymers, the stress-to-strain ratio is definitely not linear. Further, the recorded strain is a function of the time allowed under load; and the material may not promptly return to the same unloaded length. Because of the last, it is definitely not proper to call the modulus one of elasticity. As a substitute, one could construct a modulus of extensibility, which would be the reciprocal of what is usually called the modulus of elasticity. On the thesis that there has been no internal change in the material because of the stress, and that the original internal architecture will be precisely restored after load release, the physicist continues to use a modulus as a proper expression of extensibility even with polymers. To emphasize the fact that the modulus calculations are based only on the values seen during extension, rather than during the elastic recoil, I have used the symbol S rather than the conventional E in all the equations presented below. It should be obvious that one must append to any modulus calculation a careful descrip-

tion of the stress used and the time over which it acted. This has seldom been done. A derived slope obtained by the use of a conveniently large stress, because of the nonlinearity of the stretch curve, often has no counterpart in this curve—the modulus represents a mathematical figure only.

Evidence presented above leaves room for doubt that the internal structure of a vascular tissue is necessarily the same, just because the unloaded diameter might be restored. This restoration might involve muscle contraction, or it might be due to a passive creep recovery. Even in the latter case, an architectural rearrangement conditioned by the stretch might still be present. We have seen that, with enough load, the contracted ring may start from a smaller diameter but reach the same stretched value as an unstimulated one. Shall we, from the calculated modulus value, deduce that the tissue has been weakened because of the muscle contraction? We have seen that with aging the unloaded diameter tends to increase—an increase which may or may not be at the expense of the elements which condition the major portion of wall extensibility. Here, a calculated modulus value might seem to be evidence for a wall stiffening, which may or may not have developed. In those cases where the slope of the pressure-volume curve remains unchanged, we may seriously doubt that the increased modulus value is an overly meaningful index to wall stiffness.

The claim is often made that the increase in diameter is a way of compensating for a wall stiffening with age. This statement arose from the modulus formula itself. If the ratio of $\Delta P/\Delta l$ remains constant, the volume uptake for a unit length of vessel remains constant, and the change in initial diameter can hardly be said to be a compensation at all. Actually, as will be discussed later, the diameter change will affect the propagation velocity of the pulse wave, which will affect the length of vessel that is receiving volume at any given time interval. Thus, indirectly, some compensation for a wall stiffening might be effected, but it is questionable that this effect can be stated in quantitative terms, and any such formulation certainly would not use the same equation as is used for a modulus calculation. For the time being, it appears essential that before we can talk in meaningful fashion about changes in stiffness of the wall, a change in the actual slope of the pressure-diameter or pressure-volume curve alone must be shown. It is on this last point that the evidence on the effect of aging seems to be weakest.

Since, when one is working with a vessel during life, the stretch does not start from an unloaded size, another modulus has often been substituted, in which the diameter change is related to the real size seen just before the new increment in stress was applied, i.e., the diastolic diameter. This modulus is just as justifiable as that given above, but its value must be quite different. One can be converted to the other arithmetically only if the tension-length relation is linear. Unfortunately, the two moduli have too often been treated as interchangeable. Finally, since changes in pressure and volume are usually the primary data in the living aorta, a modulus based on the pressure-volume relation has been substituted. Conversion of this modulus to that using tension and length is quite complicated. Perhaps the interrelations could be best expressed in terms of their derivations:

Young's modulus (length) is the applied force per unit area divided by the proportionate length change. For a circumference increase, the area over which a given load is applied will be the length of the ring (l) times the wall thickness (a). The strain will then be the relative increase in circumference, i.e., $2\pi\Delta r/2\pi r$, or $\Delta r/r$. Since the material is being stretched from an unloaded state, the applied tension will be ΔT , and r will be r_0 .

Thus

$$S_0 = \frac{\Delta T}{\frac{\Delta r}{r_0}} = \frac{\Delta T r_0}{\Delta r} \quad (1)$$

If the change in radius and in tension are small enough that they lie on the actual stretch curve, the equation can be written as

$$S_0 = \frac{dT r_0}{dr} \quad (2)$$

This derivation assumes that there will be no significant change in length or in wall thickness accompanying the radial stretch, which, with large diameter changes at least, is certainly not true, as will be discussed later.

Now let us suppose that the initial radius is not the unloaded value, but is taken when the tissue is already under stretch. The basic equation would not be altered:

$$S_d = \frac{\Delta T r_d}{\Delta r} \quad (3)$$

but the value for S_d would not be the same as that for S_o . If the changes are very small,

$$S_d = \frac{dT r_d}{dr} \quad (4)$$

Next, let us express the stress in terms of pressure. This is usually done by taking the pressure (P) as equal to T/r (21). As pointed out by Frank (29), and stressed recently by Peterson *et al.* (91), when the wall is relatively thick in relation to the internal radius, the more proper expression would be $P = Ta/r$, where a is wall thickness. With an imposed stretch: $P + \Delta P = a(T + \Delta T)/(r + \Delta r)$. When $P = 0$ and $T = 0$, this becomes $\Delta P(r_o + \Delta r)/a = \Delta T$. Substituting for ΔT in equation 1:

$$S_o = \frac{\Delta P(r_o + \Delta r)r_o}{a \Delta r} \quad (5)$$

If Δr and ΔP are very small, their product will be infinitesimal, so that

$$S_o = \frac{dPr_o^2}{a dr} \quad (6)$$

And from equations 3 and 4 we obtain:

$$S_d = \frac{\Delta P(r_d + \Delta r)r_d}{a \Delta r} \quad (7)$$

and

$$S_d = \frac{dPr_d^2}{a dr} \quad (8)$$

Now to express the radius change in terms of volume:

$$\begin{aligned} V &= l\pi r^2, \text{ and } V + \Delta V = l\pi(r + \Delta r)^2 \\ &= l\pi(r^2 + 2r\Delta r + \Delta r^2), \text{ or} \\ \Delta V &= l\pi(2r\Delta r + \Delta r^2), \text{ or} \\ \Delta r &= \frac{\Delta V}{l\pi(2r + \Delta r)} \end{aligned}$$

Substituting for Δr in the denominator and then for $l\pi r^2$ in the numerator of equation 5:

$$\begin{aligned} S_o &= \frac{\Delta P(r_o + \Delta r)r_o l\pi(2r_o + \Delta r)}{a \Delta V} \\ &= \frac{\Delta P(2l\pi r_o^3 + 3l\pi r_o^2 \Delta r + l\pi r_o \Delta r^2)}{a \Delta V} \\ &= \frac{\Delta P(2V_o r_o + 3V_o \Delta r + \frac{V_o \Delta r^2}{r_o})}{a \Delta V} \\ &= \frac{\Delta PV_o(2r_o + 3\Delta r + \frac{\Delta r^2}{r_o})}{a \Delta V} \end{aligned} \quad (9)$$

and

$$S_o = \frac{2dPV_o r_o}{a dV} \quad (10)$$

Substituting for Δr in the denominator of equation 7, and following through as in equations 9 and 10:

$$\begin{aligned} S_d &= \frac{\Delta P(r_d + \Delta r)r_d l\pi(2r_d + \Delta r)}{a \Delta V} \\ &= \frac{\Delta PV_d(2r_d + 3\Delta r + \frac{\Delta r^2}{r_d})}{a \Delta V} \end{aligned} \quad (11)$$

and

$$S_d = \frac{2dPV_d r_d}{a dV} \quad (12)$$

A commonly used, but incomplete, modulus (see equation 7) is:

$$S_d' = \frac{\Delta P r_d}{\Delta r} \quad (13)$$

And another (see equation 11) is:

$$S_d'' = \frac{\Delta PV_d}{\Delta V} \quad (14)$$

The relationship between these moduli could be illustrated by taking a hypothetical tube with an unloaded radius of 10 mm, in which the radius increased 1 mm for each 1 g per cm² increase in tension. The stress-strain relation will then be as shown in figure 2A. The value for the modulus (equation 1) would be 10. The calculated pressure-radius and pressure-volume curves would not be linear (fig. 2B and C).

A modulus calculated on the basis of a loaded initial radius (equation 3) will increase as r_d increases (table 1). A modulus based on pressure change would give the constant value of 10 if equation 5 is used, but if equation 6 is employed, the S_o value decreases as the strain becomes larger, so that even a 1 per cent change in strain produces a decreased value. Curiously enough, the value of S_d calculated from equation 7 shows a constant value, while that from equation 8 progressively decreases.

Converting the radius changes to volume increases makes the formulas very cumbersome. Once again, equation 10 gives a changing modulus for S_o , as does equation 12 for S_d . There is no simple way of converting the moduli values obtained from the different formulas to each other.

Based on studies with rubber, King (62, 63) introduced another measure of extensibility, β , which is the ratio of the unstretched length L_o to the maxi-

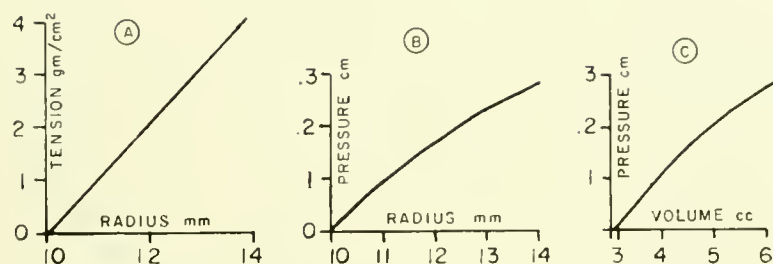


FIG. 2. Extensibility and derived distensibility relations for a hypothetical tube showing a linear tension-length relationship.

TABLE I

| T g/cm ² | r mm | P cm $\times 10^{-2}$ | V cm ³ | S_d (3) | S_o (5) | S_o (6) | S_d (7) | S_d (8) | S_o (9) | S_d (12) | S_d' (13) | S_d'' (14) |
|--------------------------|-----------|----------------------------|------------------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|----------------|-----------------|
| 0.1 | 10.1 | 9.9 | 317 | 10.0 | 10.0 | 9.9 | 10.0 | 10.0 | 21.0 | 20.6 | 9.9 | 10.3 |
| 0.2 | 10.2 | 19.6 | 326 | 10.1 | 10.0 | 9.8 | 10.0 | 9.8 | 10.6 | 6.9 | 9.8 | 3.3 |
| 0.3 | 10.3 | 29.1 | 333 | 10.2 | 10.0 | 9.7 | 10.0 | 9.9 | 10.1 | 9.0 | 9.7 | 4.4 |
| 0.4 | 10.4 | 38.5 | 340 | 10.3 | 10.0 | 9.6 | 10.0 | 9.8 | 9.7 | 9.2 | 9.7 | 4.5 |
| 0.5 | 10.5 | 47.6 | 346 | 10.4 | 10.0 | 9.5 | 10.0 | 9.8 | 10.0 | 10.6 | 9.5 | 5.2 |
| 1.0 | 11.0 | 90.9 | 382 | 10.5 | 10.0 | 9.1 | 10.0 | 9.5 | 9.7 | 8.8 | 9.1 | 4.2 |
| 2.0 | 12.0 | 166.7 | 452 | 11.0 | 10.0 | 8.3 | 10.0 | 9.2 | 10.0 | 9.0 | 8.3 | 4.1 |
| 3.0 | 13.0 | 230.8 | 532 | 12.0 | 10.0 | 7.7 | 10.0 | 9.2 | 10.0 | 8.2 | 7.7 | 3.6 |

imum extension possible. Hence $\beta = L_o'/(L_{\max} - L_o)$. If a proper L_{\max} can be determined, this ratio has several advantages, but it also suffers from the same uncertainty as to what a proper L_o value should be, particularly if, in constructing the relationship, the tissue has been stretched so as to approach L_{\max} .

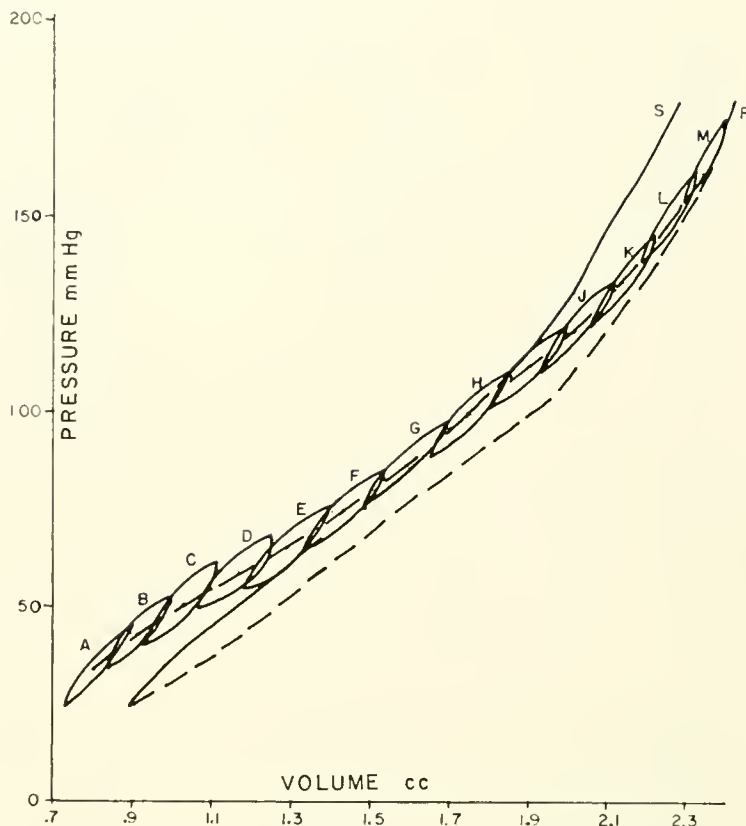
It has become common to compare a "dynamic" modulus, as obtained with rapidly repeated small stretches, to a "static" modulus. For example, Lawton (77) and Cope (22) reported a small increase in the dynamic value over the static for the aorta, which presumably reflects the influence of the rate-dependent factors involved in the visco-elastic behavior. But there is confusion as to how a static value should be determined. Sometimes values taken from a single continuous stretch curve covering the whole range of physiological pressures are used if the involved stretch has been done slowly. In other cases, a pressure-length value representing the center of the dynamic loop is taken as indicating the static value. Only rarely does this give a value different from one based on the peak values of the loop, and it would appear to strain the definition to take this as a static value at all. A third method is to hold a peak load constant until, through creep, the length has approached a final value. All three methods give different values, which simply indicates again that more than viscosity is concerned in tissue hysteresis. This can be illustrated by an experiment shown in figure 3. An isolated ring of dog thoracic aorta was first subjected to a continuously increasing stretch,

over 2 min, to a high tension. Tension was converted to pressure, and half-circumference to volume. The peak tension thus represented a pressure of 350 mm Hg. The load was then slowly released, over 2 min, and, as before, the ring did not return to the same initial volume setting. A second identical stretch (in terms of tension) was then made. The relations obtained during this second stretch and stretch release are plotted as the solid line in the figure. This stretch curve is not different from those we have used in the past to classify the distensibility of aortic rings. Now the ring was allowed to remain in Locke-Ringer's solution for 2 hours, during which time the unloaded volume was very slowly decreased. It was mounted on the stretching apparatus, care being taken not to stretch it in the process. A small length change was then made rather rapidly (0.1 sec), and the stretch repeated in rapid succession ten times. Stable stretch and stretch-release curves were established by this time. The pressure-volume relations of this stable loop are given in the figure as loop A. The same stretch was then performed an 11th time, but the peak value was held constant for 5 min, allowing the pressure to fall to its static value, some 2 mm Hg lower. The ring was then returned to a volume setting part way up the original loop, and a new series of rapid stretches made, the last loop being shown as B in figure 3. Again a static pressure was obtained. The whole process was repeated 13 times.

The initial volume for the loops was first smaller



FIG. 3. Pressure-volume relations for a ring of dog thoracic aorta, in situ length 10 mm, with stretch done by continuous stretch (curve *S*) and by successive, repeated dynamic stretches. The broken line, curve *R*, is the stretch-release curve for the continuous stretch. The crosses mark the mid points of the successive hysteresis loops. The solid points represent the postdecay (static) tension values reached 5 min after completion of the stretch.



than that given by the continuous curve, but crossed it and became greater at high pressure levels. The continuous curve reflected the large stretch which had preceded it. If less load had been used for this stretch, the curve would have differed less at low pressure settings, but even more at high pressures. It might seem that a pressure-volume curve obtained by joining the midpoints of the respective loops might give a better measure of aortic distensibility. But, in life, the aorta is never free from stretches, and any departure from normotensive pressure levels is but temporary. We would expect, then, that when the pressure did fall below normal, the aortic volume would be greater than indicated by this curve constructed from the loops.

More important, the volume change (ΔV) for the different pulse pressures was almost the same for the different loops as when taken from the continuous curve. This is particularly true in the normotensive pressure range. Hence, the very different methods of stretching produced some, but not large, changes in the $\Delta P/\Delta V$ value. Now let us express these distensibility curves in terms of moduli, using equation 14. As shown in figure 4, the dynamic S_d for each of the loops, using the peak value only, was greater than

the static by an average of 10 per cent. The continuous stretch curve gave modulus values varying from -15 to $+12$ per cent of the static, with an average difference of $+2$ per cent. Also shown in figure 4 are the modulus values calculated for only the very first part of the stretch curve for each of the loops. The fit with the other moduli is erratic, but the values are considerably greater than those based on peak values. These results are given in detail only to illustrate how difficult it is to classify the behavior of the aorta on the basis of any single technique of performing stretches.

Changes in Length and Wall Thickness of Arteries

In all modulus calculations, it is unrealistically assumed that length and wall thickness remain constant. Lawton (76) presented evidence that the volume of the aortic wall remained unchanged during a stretch. This means that as the circumference increases, there should be either a shortening in length or a decrease in thickness. Fenn (26) and Fawcett calculated that if the wall is isotropic, there should be no length change, so that only wall thickness would be involved. A direct recording of the

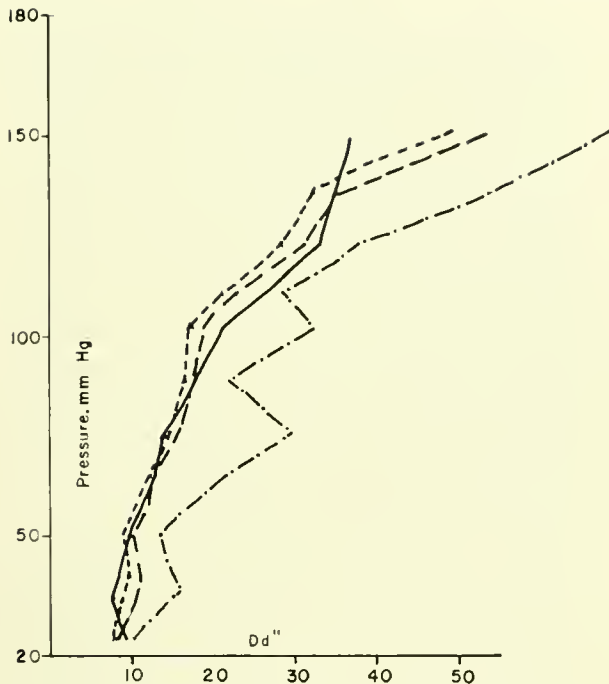


FIG. 4. Distensibility modulus (eq. 14) calculated from the data of fig. 3. Solid line, from continuous stretch curve. Dotted line with dots, from peak values for hysteresis loops. Dotted line with triangles, from postdecay (static) values for loops. Broken line, from initial slopes of stretch curves of hysteresis loops.

change in thickness during a stretch has not been made. There are some sparse references to the relation of the unloaded thickness (a) to the outside diameter (D). Thus King (62) found an a/D ratio of .09 for human aortas. McDonald (84), in a survey of many arteries from the dog, found a constant ratio of .08. In studying the effect of age on the human aorta, King (64) found a progressive decrease in thickness, so that the product of thickness and radius was nearly constant. On the other hand, young aortas show more longitudinal retraction upon excision than do those from older people (107), which might account for part, at least, of the difference in wall thickness. The question of how much the wall thins during a stretch needs documentation, since this factor will affect the derived modulus value.

In isolated vessels subjected to a volume increase, Fenn found a lengthening, from which he concluded that the wall was anisotropic (26). McDonald (84) is quite correct in emphasizing that the longitudinal extensibility observed in isolated vessels may not be a measure of changes that might take place in the in situ vessel under longitudinal restraint. Hence if the intact vessel is in the steep portion of the longi-

tudinal extensibility curve, its length changes with each pulse would not be large. The presence of the aortic sheath might also reduce length change in the in situ aorta. It is of interest here that a pulmonary artery freed from surrounding connective tissue showed a longitudinal thrust with a volume injection, while one still bound showed but minor change (32). Yet the vessel wall should not become anisotropic simply because it was released from its longitudinal restraint. Length changes in living animals have not been completely measured. Lawton (78), working with serial photographs of a dog abdominal aorta, found a small shortening in early systole and a lengthening in diastole. This made the length and circumference changes almost 180 degrees out of phase. Similar length changes for the abdominal aorta were found by Patel and co-workers (87). In contrast, they found length and diameter changes to be in phase in the thoracic aorta.

The small length changes recorded seem in sharp contrast to the sometimes rather striking longitudinal thrusts seen in the aortic arch. And at times a freed carotid artery, or more rarely a femoral artery, visually seems to be showing a length change. These thrusts might reflect factors other than a distention upon invasion by the pulse wave, however. The heart is anchored in the chest by the large vessels. It has long been known that the base of the heart is lowered in contraction, which must serve to lengthen the aorta and pulmonary artery (47). Rushmer (113) has described this movement as starting in the period of isometric contraction. The motion of the arch, and of the brachiocephalic arteries which serve as anchor points for the arch, would reflect not only the geometry of the vessels but the firmness of attachment of the descending arch to the body wall. Further, respiration displaces the aorta, which acts as though it is bound rather firmly to the diaphragm. These longitudinal thrusts would bear no necessary time relation to the arrival of the pulse wave, and a deciphering of the origin of length changes in a vessel may not be easy.

Considerable confusion was raised by a report (113) that when diameter and pressure were simultaneously recorded in the thoracic aorta, an unorthodox hysteresis loop was obtained in which, during stretch, the diameter change was proportionately greater than the pressure change. These loops were taken from an oscilloscope. Inspection of the individual diameter and pressure records indicates that the whole of the diameter curve simply preceded the pressure curve (126). If the two were superimposed,

ignoring the time lag, the expected hysteresis loop, although small in magnitude, was seen. Maintenance of strict identity between the site of measurement of the two variables is difficult at best. If there has been a longitudinal displacement of the aorta, and hence of the circumference recorder, through influences other than the arrival of a volume pulse, a seeming "phase lag" between the two recorders could be produced.

Curiously enough, with isolated strips of arteries, the time lag is reported in the opposite direction for pressure leads. From this lag is calculated the viscous component of a dynamic modulus (48, 84).

Summarizing, we can say that despite many studies on the extensibility of the aorta and large vessels, it is still uncertain whether the presented stretch curves may be reflecting to such a great degree the techniques used that they are not readily illustrative of the characteristics of the wall. Work of the future will certainly be concentrated on measurements made on living vessels, that will include not only diameter change but changes in length, and perhaps in wall thickness. There are not sufficient data to allow a well-based speculation as to how the *in vivo* measurements might fit with those obtained from isolated specimens. The question of how muscle contraction might affect tissue extensibility, for the aorta and for the muscular arteries, is yet to be definitively answered. Whether an expression of extensibility in terms of a modulus is the most satisfactory tool remains questionable.

ACTION OF THE AORTA AS A CONDUIT

Pulsatile Flow in Rigid and Distensible Tubes

Since the aortic flow is never steady, we can turn immediately to a consideration of pulsatile accelerations and decelerations rather than deal further with the classic hydrodynamic equations. As a start, let us visualize a piston pump connected to a rigid pipe of uniform bore, with the piston being driven by a large force. Let us leave the distal end of the pipe open, so that a flow through can be established. Also, let us imagine a valve system so constructed that the barrel of the pump can be filled, during piston withdrawal, from an external reservoir. To start a pump cycle, the first tiny forward movement of the piston will produce a compression of the adjacent fluid. This initial compression will represent a high pressure—one that cannot be recorded, since any manometer used would

of necessity have a membrane, the resistance of which toward displacement would be less than that of the fluid or the rigid pipe walls. Once the involved force is sufficient to overcome the frictional resistance to fluid displacement, or to overcome the inertia of the fluid column, flow can start. While the time interval between may be short, we can say that there will always be a temporal separation between the creation of the pressure force and flow through the tube. This is commonly spoken of as a phase lag, with pressure leading. The definition of the physical forces and the quantitation of such lags, for both rigid and distensible systems, have occupied the attention of many physically minded workers of late (33, 48, 54, 60, 70, 85, 139). I do not consider myself qualified to judge the relative contributions of these papers.

Now let the piston complete its stroke, and reverse. The pressure in the pump will show a sharp fall, the amount depending upon the speed of inflow from the side reservoir. Since a pressure gradient has been previously constructed in the pipe to produce displacement toward the open end, or, if preferred, since fluid has already been accelerated toward this end, flow will continue for a brief interval despite the pressure fall in the pump. Once again, then, we have a phase lag, and the fluid column can be said to have an inertial force. If the pump strokes are repeated at a rapid frequency, the flow per cycle will be related to how well matched the duration of each phase of the pump cycle is to the phase lag, as set by the frictional and inertial characteristics of the tube. This principle of matching can be illustrated by another model. Suppose a U-tube mercury manometer is made to oscillate by a periodic blowing of air into a side arm on one side of the U-tube. The first buildup in air pressure will displace the mercury, and after this the mercury column will oscillate back and forth, the period being conditioned by the size of the tube and the other components of fluid resistance to flow. If the frequency of the air puffs matches that of the mercury column, the excursions will be reinforced. Conversely, if the generating frequency is out of phase with the mercury oscillations, movement of the mercury, or "flow," will be minimal.

Equations which relate flow to pressure usually express the phase lag in terms of a component of the frequency of the repeated strokes. This is simplest if the pressure buildup by the pump has a sinusoidal form. If the stroke is of a different form, the pressure curve is broken down into terms of a fundamental sine wave and a number of superimposed harmonics.

Matching with the resonant characteristics of the fluid-filled tube could be either with the fundamental wave or one of the prominent harmonics.

Use of the same pump coupled to a distensible tube of uniform bore and wall extensibility will present a somewhat different pattern. Because the wall can yield, a large part of the energy imparted by the piston can cause an increased tension in the tube wall. It is no longer necessary to construct a pressure sufficient to overcome the resistance of the whole fluid column, for as soon as the fluid resistance to displacement in the first small segment of tube is overcome, piston movement can displace volume into this segment. The pressure energy of this fluid will go into a stretching of the walls of the segment. If the wall extensibility is great (as with condom rubber), the first segment could accommodate all the fluid displaced from the pump, and there would be no appreciable pressure rise in the tube and no flow through its length. It might be pointed out that the molecular movements in this wall stretching are directed toward the side of the tube, so that the displacement pattern is more like that of turbulent flow in a rigid pipe than that of streamline flow.

If the tube is less distensible, only part of the fluid compression transmitted to the first segment will go to produce wall extension, for the fluid must retain enough pressure to prevent the elastic recoil of the stretched walls. This erects a pressure differential between the first and next segment of tube, a differential related to wall elasticity (which need not be identical with wall extensibility) and the fluid resistance of the second segment. When the differential becomes larger than the resistance, fluid displacement will follow. In a tube of uniform distensibility, then, except for the frictional energy dissipation, the same volume will be accepted, per unit length of time, by each successive tube segment as the first part or front of the wave moves through the tube. Hence, if the piston displacement is linear against time, the pressure in the pump and the upper part of the tube will simply remain constant, since all the pump outflow will be taken to establish the wave front as it moves from segment to segment through the tube. This pattern of a constant pressure can be demonstrated in a rubber-tube model. As the pressure front moves, flow through the stretched segments behind it will be streamlined. While the frictional cost of such movement will be small, the further the wave progresses the greater will be the cumulative energy dissipation. This analysis also means that once fluid displacement into the first tube segment occurs, the

first part of a pressure wave has been created. This wave will continue to move through the tube whether piston movement continues or not. Further piston movement does act to support the later parts of the wave, or to broaden it in time.

A sinusoidal piston movement leads to a rising and falling pressure in the upper end of the tube. This produces a pressure wave, positive or negative, which is propagated back and forth through the tube. No matter in which direction waves may be traveling through the tube, the pressure in any one tube segment at a given time simply reflects the balance between the amount of fluid entering it and that leaving it. The extensible tube should show a phase lag, too, but since only tiny segments of tube, acting more or less independently, presumably are involved, the resistance to fluid movement out of the pump should be very small. Hence a phase lag should also be small. It is well to note here that the loss in pressure in the aorta, due to frictional dissipation, is within the error of recording.

Our model of a tube with uniform distensibility has no counterpart in the arterial bed. Figure 5 shows four drawings taken from an earlier analysis of this problem (94), based primarily on the extensibility values given by isolated rings. That on the upper left depicts a part of the arterial bed of a dog, drawn to scale in respect to anatomical length and cross-sectional area at a pressure of 100 mm Hg. But in describing fluid displacements, we are more concerned with the propagation time of the pulse wave through a region than we are with actual length. The natural pulse wave moves slowly in the upper aorta, more rapidly in the lower aorta, and faster yet in the large arteries (10, 24). Suppose we redraw the figure so that the length now represents the distance traversed by the wave in a unit length of time (lower left). Next, since the pressure rise in the parts of the bed will be set by the segmental distensibility (neglecting wall hysteresis), let us redraw the figure (upper right) letting the assigned width represent the distensibility, expressed as $\Delta l/\Delta P$, rather than the cross-sectional area. Lastly, if frictional resistance is to be discounted as of small amount, we can neglect the effect of tube diameter per se, and group together into a single composite tube all vessels which might lie at the same time distance from the heart (lower right). Such a theoretical tube has a funnel shape, distensibility being great in the top (ascending aorta) and tapering down gradually to the stiff vessels that are farthest from the heart, those of the hind legs.

A linear piston displacement into such a tube will

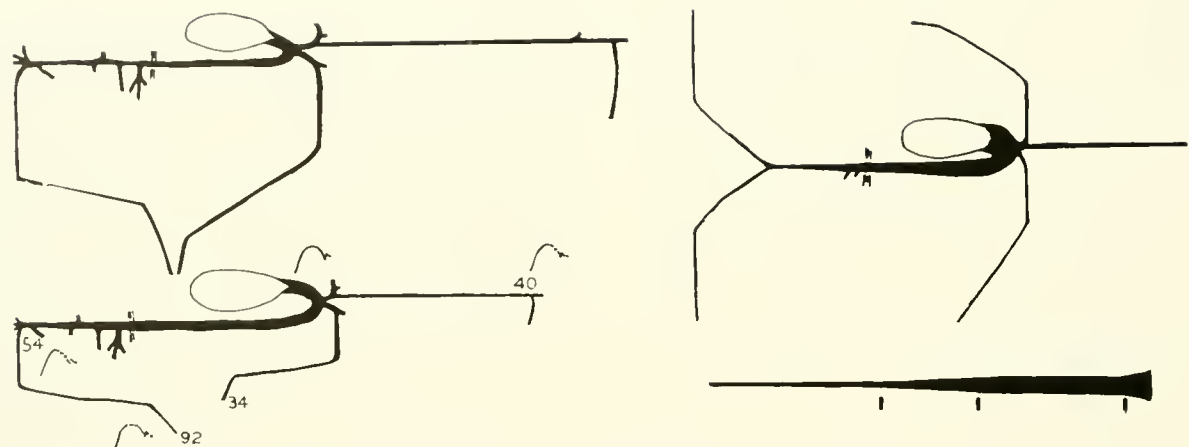


FIG. 5. A reconstruction of the arterial reservoir of the dog. [From Remington (94).] For description, see text.

no longer produce a constant pressure in the upper end. The lower part of the tube will require less fluid to construct the same pressure rise. Hence the pressure in the pump will continue to rise as the wave front moves through the tube, the pressure rise being a function of the distensibility of the lower part of the funnel. This increased pressure at the upper end will also be propagated, so that we are now creating a whole pressure wave.

Quantitation of Fluid Displacement and Wall Distensibility Relationships

The propagation of the wave front is really the same as the initial displacement of fluid from segment to segment in the tube. The rate of this displacement should be a function of wall distensibility, and it should be possible to formulate the relationship in quantitative terms. This is another case where the textbooks have such a formula so well established that it has assumed the nature of a physiological law. The supporting evidence is far from adequate. Discounting all friction and other resistance factors, Korteweg presented a theoretical formula, and Moens (see 46), working independently, arrived at almost the same formula on the basis of experiments done with various distensible tubes. The latter used artificial waves which were relatively slow in their rate of pressure rise, and he used not the first part of the pressure wave for his measurements of wave velocity, but the time interval between successive peaks as the whole wave was propagated back and forth through his closed end system. His formula differs from that of Korteweg in that he had a constant of 0.9. We have shown (46) that the velocity of the peak of such

artificial wave is less than that of the start, by a factor not greatly different from Moens' constant. Using the Korteweg formula, then, the velocity of the wave foot (v) is related to an "elastic modulus" (E) of the tube, and the density of the contained fluid (ρ), thus:

$$v^2 = \frac{gEa}{2r\rho}$$

where g is the gravitational constant and a is the wall thickness. Neglecting hysteresis, E would be the same as S_d of equation 4 derived above. Hence by substitution:

$$v^2 = \frac{ga dT_d}{2r_d \rho dr} = \frac{ga dT}{2\rho dr} \quad (15)$$

If ρ is regarded as a constant, and given the value of 1.055 for blood, and a is taken as unity, then

$$v^2 = \frac{9.3 dT'}{2 dr} = \frac{4.65 dT'}{dr} \quad (16)$$

where T' is the tension per unit length of tube. Similarly, from equation 8:

$$v^2 = \frac{ga dPr_d^2}{2r_d \rho a dr} = \frac{4.65 dPr_d}{dr} \quad (17)$$

and from equation 12:

$$v^2 = \frac{ga 2dPV_d r_d}{2r_d \rho a dV} = \frac{9.3 dPV_d}{dV} \quad (18)$$

This equation 18 is the same as that derived by Bramwell & Hill (15) and has since borne their name. They further corrected the constant by multiplying it by the weight of mercury, so that pressure

would be in terms of mm Hg. Hence their formula reads:

$$v^2 = \frac{12.7 V dP}{dV}$$

Bramwell and Hill did not use the first slope to determine dP and dV , but appreciable increments in pressure and volume instead. Commonly the pressure increment is taken to be the pulse pressure, which strains the use of even ΔP . Because our methodology is not adequate to give dP and dV values, we have no right to use the above equations. If, instead, the formula is derived from equation 11:

$$v^2 = \frac{g \alpha \Delta P V_d (2r_d + 3\Delta r + \frac{\Delta r^2}{r_d})}{2r_d \rho \alpha \Delta V}$$

$$= \frac{12.7 \Delta P V_d (r_d + 1.5 \Delta r + 0.5 \frac{\Delta r^2}{r_d})}{r_d \Delta V} \quad (19)$$

Actually, $\Delta r^2/r_d$ is so small it can be practically neglected, so that

$$v^2 = \frac{12.7 \Delta P V_d (1 + 1.5 \frac{\Delta r}{r_d})}{\Delta V} \quad (20)$$

Validation of these formulas has centered on the Bramwell and Hill equation. The earlier results, which have been reviewed (46), offer no clear evidence that the velocity of artificially generated or natural pressure waves shows either a quantitative or qualitative agreement with values predicted by the formula, when it is applied to stretch data taken from isolated vessels. The solid line of figure 6 shows an average relation of pulse wave velocity to diastolic pressure for some 200 pulses of a living dog, taken from the aortic arch to the diaphragm. The broken line shows the velocity calculated, using equation 19, from the continuous second stretch curve given in figure 3. Agreement is certainly not good. If the mean slope for each loop given in figure 3 is used instead, then, as shown by the dotted lines, agreement with the actual becomes qualitatively better, with equation 20 giving a better fit than 19. But the mean slope can have little significance as far as the propagation velocities of the parts of a wave are concerned. The speed of the wave front should be dictated by the slope taken at the beginning of the stretch phase of the loop. Calculation from these initial slopes, using equation 19 (which is here valid), gives the

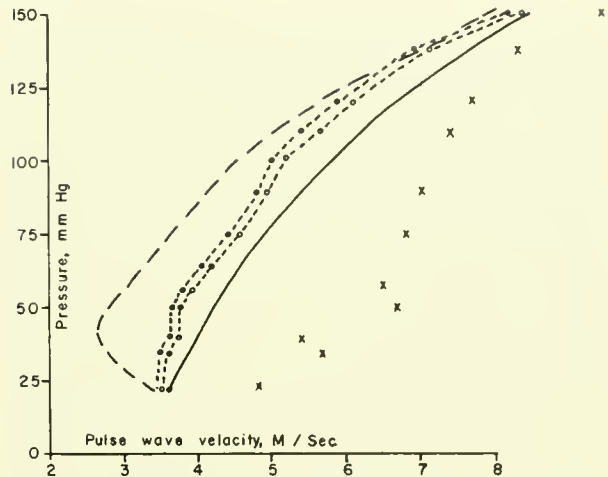


FIG. 6. Relation of pulse wave velocity to diastolic pressure. Solid line, actual values from a living dog. Broken line, calculated (eq. 19) from continuous stretch curves of fig. 3. Dotted line, closed circles, calculated (eq. 19) from mean slopes of loops shown in fig. 3. Dotted line, open circles, calculated (eq. 20) from mean slopes of loops of fig. 3. Crosses, calculated (eq. 19) from initial slopes of stretch phase of loops of fig. 3.

unconnected crosses of figure 6. These velocities are greater than the actual by 10 to 20 per cent.

In our earlier study (103), in which we compared a curve such as the broken line of figure 6 (based, however, upon a careful compilation of the stretch curves of all rings, taken in sequence, from the aorta being studied) with the actual, we believed that the underestimation would be correctable by using the slopes resulting from a hysteresis steepening of the first part of the stretch curve. The loops obtained in this earlier study were not numerous, and we did not attempt any quantitative verification of this belief. Further, and unfortunately, in this study we used both a rubber tube and the excised aorta, leaving the implication (although it very definitely was never stated) that the two behaved similarly. With rubber, the initial slope of the stretch phase of a loop proved clearly dependent on the rate of stretch. In keeping, the propagation velocity of artificial pulses through a rubber tube was found to be directly related to the rate of initial pressure rise. But with the aorta, using either artificial or natural pulses, there was no similar relation between the rate of pressure rise and the wave velocity. My more recent evidence (96) that a dependency of the aortic stretch curve upon the rate of stretch is minor is quite compatible with this finding.

A calculated velocity for the wave start, in excess of the actual velocity, may be explained by four

things. 1) The loops given by an isolated ring may be much wider than those found in the living aorta. Evidence was cited above that this might be true. 2) The velocity may be dictated not by the wall extensibility, but rather by the force of elastic recoil. Calculation from a stretch-release curve would indeed give smaller values. The question is what amount of stretch should be used to produce pertinent stretch-release curves. 3) The distensibility slope of the aorta during life may be entirely different from that indicated by the isolated rings. The data of Peterson (91), for example, seem to have it greatly different. 4) Factors which act to slow the pulse wave should be introduced into the formula. To the extent that the aorta acts as a rigid tube, fluid resistance toward flow can act in this manner, as will a phase lag between the pressure pulse and the corresponding fluid displacement. Many workers now accept the presence of an appreciable lag. As will be seen, acceptance of such a lag cannot be readily reconciled with the failure to find a correlation between wave velocity and the rate of pressure rise, as mentioned above.

Phase Lag and the Harmonics of the Arterial System

Since phase lag is formulated in terms of the frequency of harmonic components, the first step is to perform a Fourier analysis of the pressure wave. For this, a sinusoidal fundamental wave must be selected. Since such a fundamental is not readily apparent in the contour of the natural pulse wave, it is selected on the basis of a time duration (123, 124). Usually the length of the pulse cycle is used. As emphasized by McDonald in the introduction to his book (84), such a mathematical analysis can start from one of two premises. First, we can assume that each pulse is an isolated or transient phenomenon, with the aortic volume being almost static when a new cardiac ejection and sudden flow acceleration are begun. Second, we can say that the heart rate is virtually stable, so that the ventricle is repeatedly pulsing the arteries at a set frequency. The latter premise makes the cycle length a true measure of the wave fundamental, makes the harmonics relatively reproducible from beat to beat, and makes all the mathematical compilations very much easier. A change in heart rate will vary the contained harmonics and alter the phase lag between pressure and fluid displacement. It will, then, alter the wave velocity.

But the fact that an analysis on the basis of a uniform heart rate is easier to make does not mean that the premise is correct. Much evidence can be

quoted for the stand that each pulse is indeed an independent event. Strict regularity of the pulse rate is infrequent, usually being found only in rather prolonged experiments in animals under deep anesthesia. In the unanesthetized dog or human, variation from cycle to cycle is clear. In this variation the diastolic period is affected predominantly or exclusively. The pulse contour during systole, and its duration, is affected but little. Further, when the heart rate changes outside the limits of such beat-to-beat variations, systolic durations and contour are altered far less than is the cycle length (100). If the fundamental is reset each time this cycle length changes, a different harmonic picture will be required to construct the same systolic pressure contour. If the fundamental is taken as the average cycle length for a number of pulses, then we must proceed cautiously in interpreting the influence of the harmonic pattern on the contour of any single pulse of the group.

The whole approach seems more hazardous, too, when it is recalled that the length of systole almost never equals half the cycle length. This makes the heart quite unlike most pumps. Perhaps it would be more logical to use twice the length of the systolic period as the fundamental wave. This might be done for a central pulse, but certainly not for a peripheral one, where the incisura has been lost through damping.

Believing in the principle of a stable heart rate, McDonald (84) would have the velocity of the wave foot increasing with the heart rate. He offers no experimental support for the claim. We have looked often for evidence of such a dependency on heart rate and, with the single exception presented below, have not found it. However, McDonald has calculated that in a vessel the size of the aorta neither the viscous resistance factors nor the pulse frequency would affect the velocity to significant degree. In a smaller vessel, such as the femoral artery, he calculates that the viscosity would slow the velocity by about 10 per cent, and an increased heart rate might restore it to the value expected from the Bramwell and Hill formula. Much larger changes than these would be needed to correct the formula if the data given by the crosses in figure 6 are correct.

We did offer evidence (46) that a slower foot velocity was seen in the early part of the response of an animal to an injection of acetylcholine, when the heart rate was slow, than was seen later when, at the same diastolic pressure levels, the heart rate increased. A similar effect at higher pressures has

not been observed. We then attributed the velocity change not to the heart rate but to a changing hysteresis loop behavior of the wall. A long diastolic interval could allow more time for recovery after a stretch, and the diastolic size, and hence the distensibility modulus, would be thereby reduced. It is less clear now (96) that the difference in this size could be sufficient to account for the difference in wave velocity. Yet it remains possible that the correlation with heart rate was still only coincidental, and that when the pressure was abruptly lowered the slope of the stretch curve could be shallower for the first few beats than it would be after the pressure had remained low for some time.

Most especially, if we regard the pulse wave as an independent phenomenon, the velocity of the wave start would be affected least by a change in harmonic frequency. The upper parts of the pressure pulse could have their propagation speed affected to greater degree by these frequencies or by the speed of the pressure upstroke. A different velocity for the parts of the wave was fully accepted by Bramwell and Hill simply on the basis of their formula. They went further (14) and held that the difference in velocity could be such that the anacrotic rise of the pulse would progressively steepen in transit until finally the wave force would become unstable, and a "breaker" (like that seen when an ocean wave enters shallow water) would form. Evidence of such breaker phenomena was seen when pulses were generated in a bicycle tire. As will be described later, evidence is not clear that the natural pulse does so progressively steepen during propagation, and there is no evidence at all for sudden pressure vibrations that would mark a breaker. However, the calculated differences in velocity between the start and the peak of a natural wave are not large enough to create a breaker within the length of the aorta.

If there is a velocity differential between the parts of the wave (and it would appear to be quite small if present),² it could reflect the progressive increase

² There is an obvious discrepancy between the statement that there is no clear evidence for a difference in propagation velocity of the parts of a natural wave and our published results (103) which showed clear differences in transit time for the parts of an artificial wave. There are few inflections on the natural pulse form which can be measured with the necessary precision to establish a difference in propagation velocity. The start of the wave and the incisural notch can be so timed, and these two parts of the pulse contour appear to move with the same velocity. Since we have no clear idea as to which tension-length slope should be used to predict the velocity of the incisura, or to which volume on the stretch-release curve this slope should be referred, this identity of velocity with that of

in the stiffness modulus as the reference volume increases, without requiring a dependency upon the harmonic frequencies. Landowne (72, 73) did show that when small impact waves were formed at a point on the human brachial artery, the speed of their propagation was faster if they fell during the systolic portion of the pressure pulse than during the diastolic portion. The propagation velocity of these small waves was much greater than that of the natural wave. Van Citters (125) believes that the velocity is of the order to be expected if they were being transmitted by longitudinal strain through the wall itself, rather than by fluid accelerations within the artery.

Landowne (71) has also shown that, with a rubber tube or umbilical artery, either small impact waves or rapidly repeated sinusoidal waves moved at a velocity which bore a direct relation to the frequency. Our experiments showing a dependency of wave velocity upon the rate of stretch of rubber fit with this (46). The umbilical artery has a uniquely large time-dependent factor in its visco-elastic behavior (141), so that it would not be at all unreasonable that the velocity could also show a clear rate dependency. These results should not be regarded as transferable to the aorta, and perhaps not even to arteries such as the femoral or carotid. We are left, then, with the conclusion that the actual pulse wave velocity remains to be explained in a quantitative way. A mathematical analysis of the determinants of pulse wave velocity is presented in the chapter by Hardung (49).

We still have the fundamental question as to whether there would be an appreciable time lag between the pressure pulse and the fluid displacement, or the movement of the pulse wave from segment to segment through the tube. The idea of a large lag was presented first in the papers of Peterson (89, 90). He perfected a mechanism which could produce a very rapid input of fluid into the ascending aorta, and thereby generate pressure curves, of rather strange form, which were propagated. The shape of these curves was explained on the basis of a summation of three forces. First, a very small amount of fluid would be driven into the aorta more rapidly than the walls could stretch, so that, just as in a rigid pipe, there would be a sudden rise in pressure.

the wave foot may be coincidental, and not be evidence for or against a dependency of wave velocity upon frequency. It should also be stressed that while the wave parts of the artificial wave moving through an excised aorta showed different transit times, these times were not conditioned by the rate of pressure rise or fall.

This initial peak he labeled the acceleration transient, and its force was equated to the small fluid mass involved times the acceleration. Next, he added a force which increased with the velocity, representing the resistance offered to fluid displacement through the tube. This reached significant proportions only as the volume displacement did, which placed its contribution later in time than the acceleration transient. Finally, after a time lag, he added a straight line increase in pressure to represent the force necessary to prevent an elastic recoil of the walls as they were stretched.

Certainly the presence of these three forces in constructing an aortic pulse cannot be denied. The problem is to ascertain how large a role each of them plays, and how much of a time delay between them exists. Peterson's acceleration transient lasts for many milliseconds. While wall hysteresis could, to use a term employed long ago (46), make the vessel segment show a "reluctance to stretch," no studies on isolated rings indicate that the reluctance could last nearly this long. Just as crucial is his claim that the same pressure excess which marks the acceleration transient would persist through the whole systolic period, so that all the pressure pulse would have a higher value than would be predicted from a pressure-volume diagram taken from stretch data. The fact that he dealt with the whole arterial bed as a lumped system has made it difficult to follow his argument.

Rather than a discrete time lag of this sort, other workers are supporting the presence of a sinusoidal phase lag (34, 36, 83, 120, 128, 129). Using an electrical analogue, the aorta is said to have an inductive, capacitive, and a resistive impedance to flow. Of these, the inductive and resistive factors would be in phase, but the capacitive would lag up to 90 degrees. In hydraulic terms, the first of these is called inertance, which represents the mass of blood displaced into the tube segment times its acceleration. Opposing this inertance is the compliance (capacitance) reflecting the volume taken to accommodate the wall stretch, and the resistance, which represents all fluid and wall factors that cause dissipation of energy as heat. In an actual vessel subjected to pulsatile flow, the interrelation of the three would be dependent upon the rate of change in the driving pressure, usually expressed in terms of the frequencies of the harmonics. The better matched these frequencies are to the inherent frequency of the vessel compliance, which is a function of the visco-elastic properties of the wall, the greater is the flow into and through a

segment. The most proper match would be at the "resonant" frequency of the vessel.

If an isolated vessel is suddenly stretched and then allowed to vibrate, it will show a definite period of oscillation (77). This frequency will be different at various pressure levels and with different parts of the arterial system. It also can be changed by any factor which influences the visco-elastic properties. The matching frequency between a segment and the driving pressure is therefore subject to considerable variation.

But it remains uncertain why such factors should play a significant role in a distensible tube composed of tiny segments. Certainly any final analysis of the pressure-flow relation must reconcile the recent data, based on the dictum that a phase lag must be present, with the older descriptive work, which includes evidence of a general absence of effect of any physiological factor other than the diastolic pressure level on pulse wave velocity, the details of pulse contour change which takes place during propagation (to be treated later), and the actual time relation between flow and pressure curves. The last of these has been least well covered. Records of the flow pattern seen at different parts of the aorta have been presented, and such records have, superficially at least, much in common. But discrepancies exist between them in regard to quantitation, timing of peaks, and amount of end-systolic backflow. (27, 53, 56, 84, 120). Unfortunately, a simultaneously recorded pressure pulse is so rarely given that one can never be sure whether the cardiodynamic conditions were enough alike in the different experiments that one should expect similar flow curves.

In the ascending aorta, the flow rises sharply to a peak reached in early systole and then falls more gradually to reach a zero value, or below, at the time of the aortic valve closure (fig. 7). The flow then remains negligible throughout the diastolic period (119), or may show a small sinusoidal increase in diastole (131). In records taken from other parts of the aorta, the amount of retrograde flow seen just after the end of systole progressively increases as one moves out the vessel, and the diastolic wave also increases in magnitude (119).

It may be well to digress into a semantic problem that continually proves worrisome to students. The point is frequently made or implied that there is a clear distinction between the fluid displacement that accompanies the movement of a pulse wave and the "stream flow" through the vessel. In the aorta there really is no stream flow as such, and fluid displace-

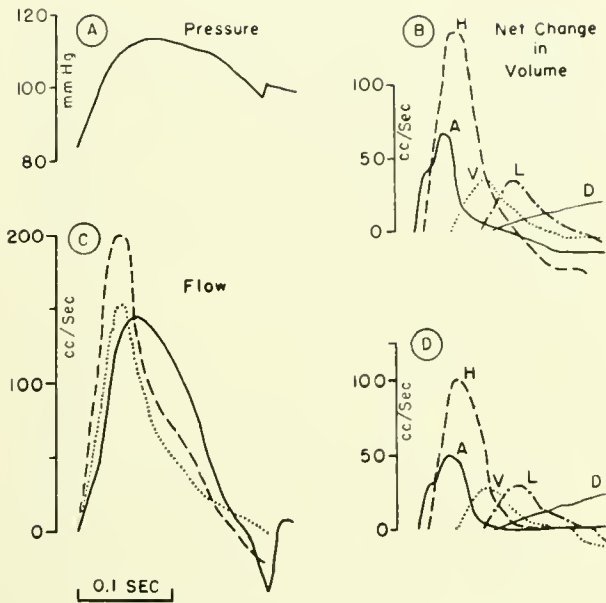


FIG. 7. Carotid pressure pulse (A) and ascending aorta flow (C). [From E. Wetterer (131).] B = change in volume uptake curves for arterial bed regions. Broken line of C = the summed uptake values taken from B. D = change in volume uptake as calculated from a hysteresis loop, as taken from fig. 3. The summed uptake values are given in C as the dotted line.

ment simply accompanies the movement of the pulse. This displacement is toward the periphery in systole, but some may be toward the heart for a period in diastole. It should not be difficult to understand that the molecules involved in such displacements in the lower aorta, for example, are not the same ones as left the ventricle during the corresponding ejection. The stroke volume is of the order of a fourth of the aortic volume. In contrast, a stream flow is established in the stiffer resistance vessels, which approach more nearly the characteristics of a rigid tube. Another way of saying this is that flow through the aorta starts and stops, rather than being continuous.

At present, the aortic flow curves available offer no clear indication of the amount of time lag between pressure and fluid displacement. Spencer (119) makes the statement that in the upper aorta pressure and flow start together, but he offers no supporting figure. If this is true, any phase lag will be based simply on a relatively slower increase of flow than of pressure. On the other hand, the left ventricle usually develops a pressure above the aortic level before ejection apparently begins, which excess is then gradually lost (98). Thus there appears to be a true time lag of about 5 msec, similar to that en-

visioned by Peterson. But a study of pressure pulses taken from adjacent parts of the aorta offers no clear evidence that a similar excess and time lag exist there. Thus, after the initial delay between ventricle and ascending aorta, the pressure pulse seems to be propagated at a steady rate through the aorta (98, 99).

At present, a major obstacle in the interpretation of the presented flow curves is a lack of a reference standard against which they can be compared. Quantitatively, the curve from the ascending aorta should integrate to the stroke volume less the coronary flow. But our knowledge of the time contour of cardiac ejection rests only on cardiometer curves, which come from open-chest animals and bear distortions that make one question the value of a too detailed study of their time-flow dimensions. Flows taken from other aortic regions can be related to the stroke volume only if one assumes a distribution of volume between the parts of the arterial bed.

Construction of a Hypothetical Ejection Curve

It might be of interest to construct a hypothetical ejection curve, derived from the contour of the central pressure pulse (104). This requires that all animals be assigned the same wave transmission time and the same arterial distensibility, the latter taken from an average of stretch curves of isolated rings. Certainly no claim can be made for the accuracy of such curves. All we do know is that the total stroke volume derived in this way usually agrees reasonably well with that given by a direct measurement (94). In this construction the arterial funnel, as shown in figure 5, is divided into segments, the lengths of which are approximately 10 msec of transmission time. The total volume uptake of the arterial region is then divided by the number of segments included, with the various segmental uptake curves starting in sequence every 10 msec. This derivation assumes that: *a*) the aortic pressure pulse, as taken from the ascending aorta, has no distortion because of a contained acceleration transient; *b*) the wall stretch shows no hysteresis lag; *c*) the control pulse is propagated as an entity, without damping and without augmentation; and *d*) there is no time lag between pressure change and the corresponding fluid displacement.

Suppose we take first the pressure pulse presented by Wetterer (131) corresponding to his ascending aorta flow pulse shown in figure 7. This pulse is obviously from an open-chest animal, the length of systole probably indicates that the animal was cold,

and the contour is not one we would regard as representative of that to be obtained from an animal in good circulatory condition. The ascending aorta and arch are taken as the first tube segment. From our tabulated pressure-volume tables (104) a volume uptake curve can be constructed for this segment in 10-msec intervals, starting at the time the central pressure pulse begins its upstroke. Because, in the Wetterer experiment, the ascending aorta had a flowmeter attached, we have arbitrarily reduced the volume uptake of this segment by one half. Rather than plotting the total uptake, only the net gain or loss of volume for each time interval is given as the solid line curve of figure 7*B*. While the pressure in this segment is still rising, the volume will be increasing. When the pressure falls in late systole, there will be a net loss of volume.

The thoracic aorta and head and foreleg arteries are grouped together in the next part of the funnel, and it takes the wave some 30 msec to move through the whole. Hence, for uptake calculation the total region is divided into three parts, displaced 10 msec behind each other. The summed net volume change for all three is given by the broken line, labeled *H*, in figure 7*B*. Next, the pressure wave invades the abdominal aorta and visceral arteries, which takes another 30 msec. The summed volume change of the three units involved is given as the dotted line (*I'*). Finally, the summed changes of the three leg vessel units are given in curve *L*. Flow through the ascending aorta must not only accommodate the volume acceptance of more distal arteries, but must supply systolic drainage through the arterioles as well. The calculation of this latter will not be gone into here (see ref. 44), but it is indicated in figure 7*B* by curve *D*. Ascending aorta flow now should equal the algebraic sum of all these curves at any given time instant. The value obtained is per square meter of body surface. It is assumed that the dog Wetterer used was medium size, i.e., had about 0.6 m² surface area. The use of this assumed value means that we should not expect quantitative agreement between the derived curve and the actual one, but only qualitative agreement. The total flow calculated in the above manner is given as the broken line in figure 7*C*. The actual curve presented by Wetterer is given by the solid line. The calculated values therefore indicate a flow increasing more steeply in early systole, and decreasing sooner and more sharply after the peak. This discrepancy in flow might have four causes: 1) the flowmeter might be slurring the actual

curve; 2) there might be a distortion of the aortic-flow curve because of vessel constriction produced by the meter; 3) there might be a true time lag, of appreciable proportions, between the pressure curve and the flow curve; and 4) wall hysteresis might change the form of this calculated flow curve. The influence of the last of these can be directly tested. If the volume uptake values are calculated from a hysteresis loop of the same pattern as those given in figure 3, the rate of volume gain in early systole would be decreased, and there would be little volume change while the pressure first starts its fall in late systole. The summed flow curve, as given in figure 7*C* by the dotted line, differs but little in form from that given by the broken line. Hence it would be difficult to reconcile the calculated curve with the actual with even a large amount of vessel hysteresis.

A similar calculation was done for the only three pulses presented by Spencer and co-workers (119, 120) which have accompanying pressure pulses. The flow recorder here was on the upper thoracic aorta, so that the uptake of the arch, head, and foreleg vessels were omitted when the volume changes were summed to give the flow curve. The same type of discrepancy between the calculated and the recorded flow pattern is again seen (fig. 8). It might be noted that these pressure pulses are unusual in that they have a very steep initial rise in pressure, with a relatively flat systolic crest. This might be evidence of an effective aortic constriction by the meter. If so, the flow profile in the lower aorta would not be expected to match the form of this pressure pulse.

On the premise that flow should lag behind the instantaneous pressure, Fry and co-workers (34) derived an equation in which the pressure difference between two points in the aorta was equated to the sum of an inertial term and a frictional resistance. Solution of their equation was achieved by use of an electronic computer. After checking their equation by use of a sinusoidal pump with a tube (rigid?), they proceeded to construct a flow velocity curve for the upper aorta, using catheter tips 6 cm apart for the pressure recordings. Not knowing the exact positions of the catheters, one is uncertain as to just what vessel segments should be included in an attempt to construct a similar flow curve on the basis of vessel distensibility. We used the whole aorta, as though we were calculating a cardiac ejection curve. Not knowing dog size or diastolic aortic dimensions, the calculated peak flow value was



FIG. 8. Pressure and flow values given by Spencer. Pulse *a* from Spencer & Denison (120); pulses *b* and *c* from Spencer *et al.* (119). Dotted line, summed arterial bed uptake values, as described in text.

arbitrarily made to coincide with the presented values. The agreement in contour between the curve presented by Fry (solid line, fig. 9) and that calculated (broken line) bears a good deal of resemblance to those seen with the actual flow curves. It should be mentioned that the differential pressure recording presented by Fry indicates a peculiarly long delay period between the two recording catheters, with a slow transmission velocity through that particular aorta (about 3 M/sec).

These constructions provide presumptive evidence, then, that there is a delay between the pressure and fluid displacement curves. There will certainly continue to be interest in the factors which contribute to this lag. Whether harmonic analysis of the pressure pulse curves may be the most profitable tool for this assessment remains to be decided. It is important that we do not let sophisticated mathematics allow us to lose sight of the basic processes by which a distensible tube seems to be filled. Volume is displaced from segment to segment, establishing and maintaining a moving pressure wave. Since the distal parts of the aorta are stiffer than the proximal, we would not expect that the pattern of fluid displacement out of the arch would be qualitatively similar to that of the pressure curve, for the amount of fluid leaving the upper aorta would be decreasing when the pressure was rising. Toward the end of systole, when the wave front has invaded the whole network of distensible

vessels, flow would fall sharply to a low level which represents mainly the drainage loss from the bed. At this time, the aorta would be behaving more like a rigid tube.

Judging from cardiometer curves, ventricular ejection starts slowly, then rapidly attains a maximal and constant rate which lasts through the first part of systole. The outflow then slows, reaching a small value some time before the valves actually close. Because the first outflow, although slow, is confined to the ascending aorta, the pressure rise produced must be relatively large. As the wave moves through the aorta, an even faster ejection rate will produce less rise in ascending aorta pressure. This tendency is in part offset by the stiffer walls of the more distal vessels. But in any aortic segment a pressure rise simply means that more blood is entering than is leaving for the more distal regions.

A pressure difference curve based upon a subtraction of pulses taken at two different sites can be misleading. Even assuming no change in contour, until the wave reaches the distal recorder the difference will be but a replica of the proximal pulse. When the pressure upstroke in the peripheral recording begins, this difference curve must show a sharp inflection and a fall, depending upon the duration of the first steep pressure rise and the separation of the recorders. As long as pressure is still rising in the proximal segment, the difference should remain slightly positive.

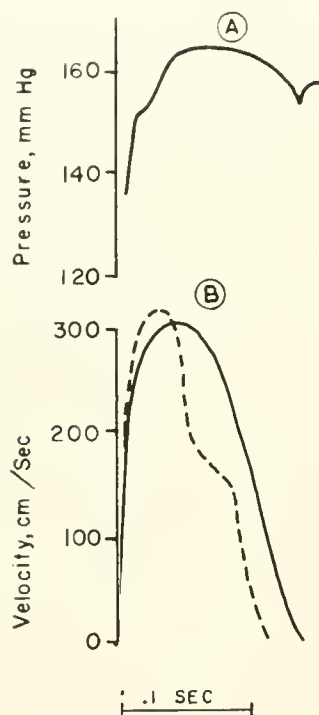


FIG. 9. Pressure and flow values given by Fry *et al.* (34). Broken line of B, calculated flow values as described in text.

When it starts to fall, the difference should swing to a negative value. This does not mean that flow down the aorta will then cease. The volume displacement is part of a wave movement, and the pressure differential simply reflects the time lag between the wave's arrival at two points in the tube. Such a continuation of fluid displacement toward the periphery, despite a negative pressure differential, could properly be called an inertial property of the fluid. What all workers are seeking is a complete description of what we mean by a wave, and what factors contribute toward its progression through the tube.

Before leaving the descriptive model, it should be pointed out that no length dimensions were placed on the tube segments that were acting independently. With wall fibers distributed longitudinally as well as circularly, there cannot be such an independence of action of tube segments. A unit of a distensible tube must have a finite length, which, however, has not been defined. This tying of segments to each other must give a distensible tube some of the characteristics of a rigid tube. However, it remains rather inconceivable that a whole aorta could act as a single bound entity, and could be given a single lumped resistance value.

To summarize this section on the behavior of the aorta as a conduit, the initiation of flow through a

rigid system certainly requires the acceleration of a whole column of fluid, an overcoming of fluid resistance for the whole length of the tube, and a phase lag between pressure built up at the generating source (pump) and the flow out the end of the tube. In such a rigid system, resistance factors can certainly be treated as a unit. With a distensible tube, however, depending upon the stiffness of the wall, only a small segment of fluid need be accelerated in any given unit of time, and the fluid resistance and the phase lag can be relatively small. A model has been presented in which a pressure wave is propagated from a minute segment of such a tube to the next adjacent segment. Of course, the tube is linked longitudinally by extensible fibers, and the length of what is being called a tube segment cannot be defined. But it is not clear that the current trend of treating pressure-flow relations in the aorta as though resistance was lumped and as though there were an appreciable phase lag between pressure and flow is helping our understanding. The propagation velocity of the wave must be linked in some way to tube dimensions and to wall distensibility, but no completely satisfactory formula for quantitating this relation appears yet to have been presented.

THE AORTA AS A BLOOD RESERVOIR

Changes in Central Pulse Contour During Propagation

In the description of how fluid displacement through the arterial bed might be calculated from the distensibility values of the various vessels, and the course of pressure change in the ascending aorta, the assumption was made that the central pulse would be propagated intact. This assumption is clearly false. The pulse contour is modified during transmission, this modification resulting perhaps from damping, or from a poor matching between the frequencies of the volume input curve and those set by the distensibilities and flow resistances of each arterial segment, or from an augmentation of "matched" frequencies, or even from superposition of a wave reflected from the periphery upon the incident wave. It should not be implied that, because pulse contours change, the whole method of calculation of the form of the cardiac ejection curve is invalid. If the contour changes do not appreciably alter the total displacement of fluid out of the ascending aorta, the total quantitation need not be greatly in error.

Contour differences between a central and a

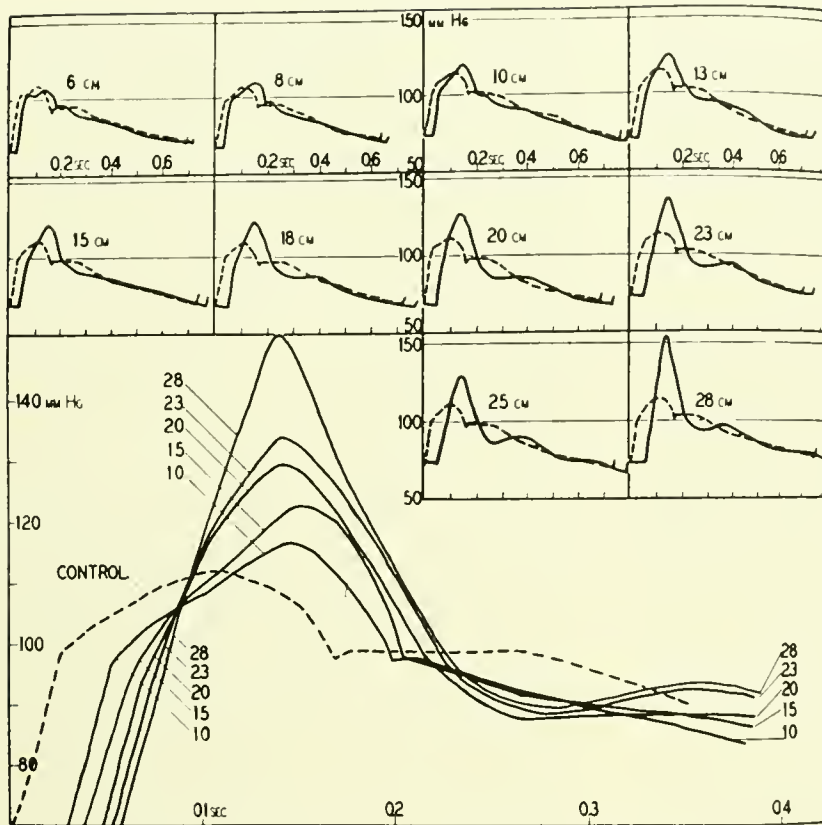


FIG. 10. Reconstruction of aortic-pressure pulses, showing comparison between control in aortic arch (dotted lines) and records taken simultaneously with their controls at indicated distances down the aorta from the arch (solid lines). Below, five of the above ten, semi-diagrammatically superimposed on a somewhat larger scale, with a representative control. [From Hamilton & Dow (42).]

peripheral pulse were recognized even in the days when pressure recordings were made using low frequency manometers. When Frank (28) developed his high fidelity manometer, he established this difference in precise terms. This was verified and amplified by the work of Wiggers and his associates (1, 135, 136) and Hamilton and his group (40, 42, 140) in this country, as well as by continued work in Europe (17, 29, 57, 58, 75, 115, 117, 133). In contrast to the broad systolic crest of the central pulse, the femoral artery pulse, for example, shows a high, narrow systolic profile. Sudden slope changes, such as the shoulder of the central pulse and the incisural notch, are no longer present in the distal vessel, having been lost through damping (fig. 10). Such damping is most obvious when the aortic pressure is low, and least obvious when the pressure is at hypertensive levels. This is probably related to the fact that the visco-elastic properties of the wall are more prominent at low pressure levels.

The changes in contour are similar to those that would be obtained if a central pressure pulse were recorded by a slow-frequency manometer system, which would allow an overswing of pressure in systole, and an exaggerated fall to a low level in early

diastole. The German workers, after Frank, have therefore thought of the portion of the arterial bed which stores blood in systole, i.e., the arterial reservoir or Windkessel, as having a lumped distensibility value, like a manometer (12, 17, 58, 132). It should be remembered, of course, that the distensibility of the arterial bed is not that of a single membrane, and it does not follow that the arterial reservoir could vibrate as a single unit as a manometer system does.

Despite much descriptive work on the contour changes which attend propagation of the pulse, our basic knowledge of the underlying principles remains incomplete. In their classic paper on this subject, Hamilton & Dow (42) presented for the first time a mapping of the changes in pulse form in the dog as recorded serially from various points in the aorta (fig. 10). This mapping reveals that as the wave moves toward the periphery the steep initial anacrotic rise remains unchanged in slope, but persists for a longer time. Hence the deflection marking its end, or the shoulder, comes at progressively higher pressure levels. The systolic peak becomes gradually narrower, so that the time from the start of the pulse to the peak is reduced. Hence, in spite of the transmission delay of the start of the wave, the peak is reached at

just about the same time in all pulses taken from the lower part of the aorta. It is most difficult to time the peak of a pulse exactly, but this approximate identity was taken as evidence that this peak was "standing." This suggests that the aorta was achieving a "resonance" with the first transit of the pulse wave.

Resonance and Standing Waves

To explain the resonance concept, let us visualize a somewhat elongated rubber balloon, filled with fluid, and connected at one end to a syringe. A sudden input of fluid would start the bag oscillating, due to a sloshing of fluid from one end to the other with a reversal of movement, or a reflection, taking place at each blind end. The period of such oscillations must reflect the time required for the fluid slosh to traverse the balloon, and therefore is related to the conduction velocity of the fluid wave and the length of the bag. The first of these is a function of the distensibility of the part of the bag through which the wave is moving, as described earlier. If the wave length of the slosh is just twice that of the transmission time through the bag (or a simple multiple of it), we could say that the bag was resonating, for *a*) the pressure changes at the ends would be just 180 degrees out of phase; *b*) the peak pressure, produced by a summing of the incident wave with the reflected wave, would be reached at the same time through half the length of the tube. This means that there would be a point of minimal pressure oscillation, or a "node," at the mid point of the tube, and all peaks and pressure troughs seen on either side of this node would be "standing" through half the tube; *c*) the time interval between two successive pressure peaks, as recorded from any point in the tube, should be a constant, and be an index to the length of tube and the wave velocity.

The records of Hamilton and Dow suggest that all three criteria can be met in the arterial system. There are pressure oscillations at the two ends of the dog aorta which seem 180 degrees out of phase, and which maintain approximately (but not exactly) the same period until they are damped out. The amount of pressure change with such oscillations is much smaller in the arch of the aorta than in the abdominal aorta, just as the distensibility of the two regions is different. There are times when all three criteria are not met in the dog, but more recent mappings indicate that what seems to be a true resonance very often is achieved (4, 101).

The carotid artery (or whole head system?) shows

no similar oscillations, or even any great change in pulse pressure with outward propagation of the pulse (39). In man, the arm system shows augmentation of the pulse pressure but not resonance as defined above (108). Records made in this laboratory indicate that the foreleg system of the dog produces pulse contour changes similar to those seen in the human arm. Further, the aorta-femoral system does not show such resonance or even clear oscillations in very small animals (140). There is question whether resonance occurs in an animal as large as man (108). The German workers do believe the human aorta to show resonance, but, as will be discussed later, their conclusion is not based on a standing peak for the peripheral pulses.

Attempts to design a model that could illustrate the prompt achievement of resonance, as occurs in the dog, have not been successful. Certainly, experiments in which independent pulses were generated in a closed and moderately long rubber tube (46) provided little insight into how it would be possible to make a previously quiet bag resonate with the first propagation of a pressure pulse through it. Granted that if the time of volume injection was made identical to the transmission time of the wave peak through the tube, reciprocal oscillations at the ends would be seen from the time of completion of the injection. But if the injection period was appreciably longer or shorter than this, there was no such immediate resonance. Instead the formed wave peak could be followed back and forth through the tube, as it was propagated at a steady rate, and reflected at each blind end. Because the wave length changed during these propagations, the foot moving more rapidly than the peak, which in turn moved faster than the "tail," after several trips through the tube the wave could finally achieve a length equal to that which would make the tube resonate. Whether a given wave ever attained such resonance would depend upon the number of trips required to change its wave length, and the number that were possible because of incomplete reflection and continued damping. The change in wave length attending propagation was attributed to the hysteresis behavior of the wall.

Similar changes in the length of an artificial pulse were seen in a tied off but in situ dog aorta (46). This change is directly opposite to that predicted by the Bramwell and Hill formula, which would have the peak moving faster than the foot. Of course, artificial waves never attained the same rate of

pressure rise seen with a natural pulse, and they were truly independent phenomena.

McDonald (84) believes that because the natural pulse is but one of a continuous train of waves with virtually identical wave lengths, each ejection could serve to reinforce the component frequency which happens to match the transmission time through the resonating part of the reservoir. This premise would permit development of resonance with the first transit of each wave. But, by extension, this premise would also require that the pulse pressure augmentation be a function of the heart rate. Again, all we can say is that neither the pressure augmentation nor the period of the diastolic oscillations has been shown to have any relation to heart rate per se when the diastolic pressure remains the same. The reciprocal oscillations between aortic arch and abdominal aorta pulses in the dog appear to be the rule and not the exception. They appear with the first beat after a prolonged cardiac arrest, as with vagal stimulation; they are not clearly accentuated at any given heart rate; it is most difficult to so alter the cardiovascular status through nerve stimulations or injected drugs as to make them disappear.

The prompt achievement of resonance by the aorta would seem to require, then, that the whole vessel could act as a unit, and "mold" any ejection wave into a pattern consistent with its own resonant properties. Alexander (7) has used the analogy of an orchestral chime, which, when struck, vibrates at a frequency set by its own geometry, unaffected by the characteristics of the impacting force. Use of this analogy is not easily reconciled with the theorem that wave propagation is from tiny tube segment to adjacent segment. Instead the pressure rise in the upper end of the aorta would have to be able, by some mechanism, to throw the whole aorta into vibrations. Yet there is no evidence that this pressure rise "signals ahead" of the propagated pulse wave. There is no pressure change in the lower aorta at the time the central pulse is first being ejected.

One question which must be decided is whether it is the propagated pressure wave itself which sets the aorta into resonance. No alternative suggestion has yet been advanced, unless one can read into a paper describing the genesis of the ballistocardiographic waves the notion that whole body thrusts might induce this resonance pattern within the vessels (43). The propagated wave in an aorta has much in common with an artificial wave being propagated through a stoppered rubber tube, although the latter does not readily create immediate resonance. The

aorta should be even less conducive to the attainment of resonance than the rubber tube. There certainly is no single reflection point, for exit vessels are distributed along the whole length of the system. One would expect, then, innumerable returning waves bearing no necessary time relation to each other. Further, the exit vessels are not blind end tubes, but continue on to become the resistance vessels of the arterial tree. This has led some to the conclusion that the aortic reservoir should be considered as more comparable to an open-end tube, the resonant wave of which would then be twice as long as that of a closed-end tube (60, 134). On the other hand, Hamilton (38) has maintained that the sudden increase in the resistance to flow in these vessels will serve to produce the positive reflection. While such reflections could take place wherever the flow pattern is changed, as at a vessel bifurcation, or even in the curvature of the aortic arch, these reflections within the tube would be small when compared to those arising from the small resistance vessels. He has documented this belief by experiments done on a rubber tube model fitted with many small rigid tubes of high-flow resistance, but with a greater aggregate cross-sectional area, placed in series with the rubber tube (41).

Alexander (1, 4, 8) recorded pulses from the arch, the abdominal aorta, and the femoral artery of dogs under a variety of physiological conditions. Usually the two peripheral pulses showed simultaneous peaks, although at times they did not. If the central pulse was subtracted from the peripheral one, to give the contour of the reflected wave, two different waves in the subtraction curve could be seen. The first of these was taken to represent the propagated peak of the incident wave, "distorted" by damping and the other factors which may give rise to contour change during propagation. The second, a swell of more sinusoidal form, was the first of the resonant oscillations. When the two waves coincided, the femoral pulse pressure was at its greatest. In some central pulses, a late systolic trough could be seen that appeared simultaneously with the distal resonant swell. When the length of the ventricular ejection period was slowed through induced hypothermia (7), this trough came far enough ahead of the incisura to be clearly recognizable.

The resonant swell obtained by such a subtraction did not have the same wave length as the central pressure pulse. In fact, there is no real evidence that the whole of the incident pulse is reflected. When subtraction curves of the same type were obtained for human subclavian pulses (108), a reflected wave

seemed to be present, but it was small in magnitude and short in duration. It was as though only the first sudden acceleration of flow produced a reflected wave. Whether this should be regarded as a common finding, true for the whole arterial tree and also for a closed-end rubber tube, is not clear.

Hamilton & Dow (42) showed that when the aorta was occluded, the frequency of the pressure oscillations seen on a pulse was more rapid than that usually found in a normal dog. By moving the point of occlusion distally, they concluded that the "end" of the resonating system must lie outside the aorta. Taking the time from the start of the central pulse to the peak of a lower abdominal aortic pulse as equal to half the total resonant wave length, they calculated that the end should be near the knee, and the node should be in the lower thoracic aorta. Wezler & Böger (134) placed the end, which they took as the point of negative reflection, in the femoral artery near the inguinal ligament in the human. Schmitt (115) located the node in the abdominal aorta in man, and the end in the distal part of the tibial artery. This was based simply on transmission times of the wave, for the time delay from the heart to the node should also equal the time from the node to the end, and equal a fourth of the total interval between successive pressure peaks of a peripheral pulse. Similar studies by Wetterer and co-workers (58, 132) placed the end of the system beyond the ankle in the foot. An occlusion by cuff inflation of the legs shortened the interval between the systolic and the postincisural pressure peaks, which they reasoned could be true only if the cuffs were still proximal to the end of the system (59). There are two aspects of studies such as these that give room for concern. First, the pressure peaks of pulses taken from the leg arteries are not coincident with those of the femoral artery (fig. 11), nor are they timed to reciprocal oscillations of the central pulse. Of the

three criteria listed above for resonance, they satisfy only one, i.e., the time interval between peaks remains about the same as that seen more proximally. It remains possible that the truly resonant pulse form could be propagated with but little distortion of time relations through the leg arteries. This seems to be what happens in the arm vessels (108). Second, occlusion of the aorta seems to make it behave as a blind-end rubber tube would, and the waves which are propagated back and forth in this occluded length of vessel do not have the same characteristics as the natural wave. It may be that leg occlusion could introduce a reflection of the wave, and change the timing between peaks, but that use of the occlusion technique to identify the end of the resonant system is not theoretically sound. It should be repeated that our studies on aortic pulses in man (108) gave no evidence of a standing peak.

Alexander (3) believed that the node for the dog was in the upper abdominal aorta where the large visceral arteries exit. This is a point of sudden increase in total cross-sectional area, where the flow rate, relative to the vessel size, accounts for a large fraction of the total cardiac output. When he occluded the visceral arteries, the frequency of the resonant waves seen in femoral pulses was increased, and the preincisural trough of the pulse of the ascending aorta became less conspicuous. Unfortunately, the pressure was also raised by this maneuver, so that the changes evoked are not indisputable evidence for his hypothesis. Conversely, an intra-arterial injection of histamine into the visceral arteries decreased the frequency of oscillations (and also lowered the systemic pressure). Ryan and co-workers (114) repeated the occlusion experiments, and concluded that the pressure rise might have been sufficient to explain the changed frequency of the resonant waves in the femoral pulse, but observed that the occlusion did eliminate the preincisural trough of the central pulse. In general, however, occlusion of exit arteries has very little influence on the timing of the pressure oscillations (57).

Alexander (4) postulated that the aorta-femoral system was essentially two open-end systems in series, the region of visceral artery exit marking an open end common to both. Arrival of the incident wave at this area would be followed by a reflection of a negative wave back toward the arch to produce the preincisural trough. The incident wave would also be propagated into the lower aorta as a positive wave. Hence the two systems would be effectively resonating with each other.

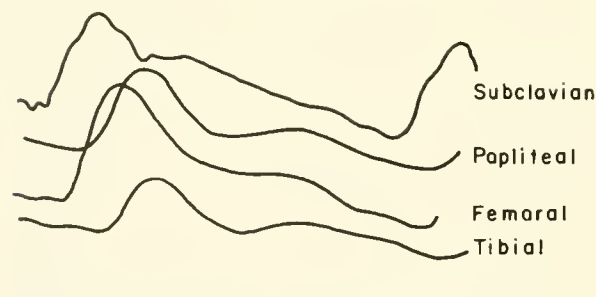


FIG. 11. Pulse contours from peripheral arteries. [Redrawn from Kapal *et al.* (59).]

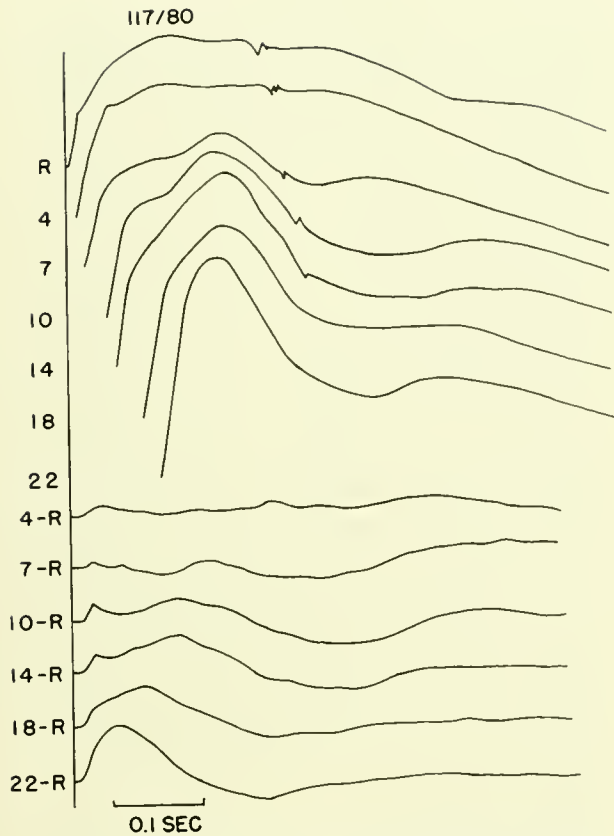


FIG. 12. A mapping of the change in pulse form in the dog aorta. Pulses from ascending aorta (R), descending arch (4), upper thoracic aorta (7), mid thoracic aorta (10), lower thoracic aorta (14), abdominal aorta (18) and iliac artery (22). [From Remington (100).]

The German workers have also been concerned about the effect the large visceral arteries might have on the resonant wave. They (58), like Hamilton, would locate the only significant reflection point in the small arteries. The influence of any single aortic branch as an independent reflection unit (particularly that of a vessel so far proximal to the "end" of the system as a visceral artery) causes them no great concern. Assuming the resonant frequency to be already established (they have presented no analysis as to how this might be achieved), they conclude that reflections in this branch would serve to augment the pressure excursion without altering the fundamental wave length of the incident wave. An example of this is seen when two manometers of different frequency response record in parallel a rapid pressure change; the records from both will be the same and reflect the response characteristics of the slower manometer. This would not explain Alexander's preincisural trough seen on the central pulse.

In a number of mappings of the dog aorta (99) I found that while in some pulses the late systolic trough could be seen, it was not present in pulses taken from the descending arch of thoracic aorta (fig. 12). Hence this trough apparently is not propagated back from the upper abdominal aorta, but rather appears *de novo* in the ascending aorta pulse. Although there were some time discrepancies between the systolic peaks of the peripheral aortic waves, there was a general tendency for a standing wave to occur. But this standing wave seemed to develop as a sinusoidal swell taking off from the broad crest of the propagated wave, and appeared first in the aortic arch or at least high in the thoracic aorta. Its size progressively increased as the wave moved toward the periphery. If this swell represented the first of a resonant wave, we would have to conclude that the node for this first peak was within the aortic arch itself. This swell developed at about the same time that the foot of the incident wave reached the femoral artery. Later reciprocal oscillations between ascending aorta and lower abdominal aorta could be seen, with minimal pressure change in the upper thoracic aorta. The node of these oscillations would thus appear to be more distal than that for the systolic peak. All that we can conclude is that the genesis of aortic resonance remains obscure.

Other Factors Which May Alter the Central Pulse Contour

Fascinating as this whole problem of resonance may be, it certainly is not the sole factor which may produce contour change and pulse pressure change when the pulse of the ascending aorta is propagated to the lower aorta or to the brachial artery. Possible factors which may bear on these changes are:

a) A loss of sharp inflections and an attenuation of the pulse pressure might result from damping. In a distensible tube such damping is due in part to fluid friction, but probably much more to a conversion of energy from kinetic to potential form because of the extension of the walls, with a delayed recoverability of this energy because of the visco-elastic properties of the wall. Clear illustrations of such a reduction in pulse pressure and lengthening of the systolic wave contour during propagation can be seen in dogs with a deteriorated circulation, or at least a weakened heart, after the use of a strong vasodilator agent (94) and when the rate of flow from the upper aorta to the lower is severely reduced, as by a partial occlusion (23).

b) A peaking of the pulse contour could follow a

speeding of the upper portions of the pulse as the modulus of extensibility is increased. This would probably cause an augmentation of the pulse pressure. This effect seemingly would be operative only if wall hysteresis were of minimal importance. However, I am not convinced that there is any difference in transit time of the wave foot and of the incisura, for example.

c) The same sort of peaking could indicate an attenuation of mismatched harmonic frequencies. If the electrical analogy is apt, there would be no augmentation of the pulse pressure in this case, however, but simply less attenuation of the matched frequencies. In a hydraulic system, of course, it might be that attenuation of one part of the pulse might yield fluid and energy for another frequency, which conceivably could produce pulse pressure augmentation. Such a redistribution of energy has not been shown to be true.

d) There could be a reflection of the whole or a part of the incident wave, whether the vascular bed did or did not achieve resonance as it has been described. The maximum possible increase in pulse pressure by reflection would be to twice the original value, which would be realized only if the whole pulse pressure showed complete reflection, and the pulse recording was very near the reflection "end" of the system. Usually the pulse pressure in a femoral artery is less than twice that of the central pulse. However, Alexander has shown femoral pulse pressures in the dog which are greater than twice the value.

e) As an extension of d), or perhaps as a result of another property of the bed entirely, when the aorta does show resonance, augmentation of the pulse pressure is appreciably greater than when a standing wave is not seen.

f) In some cases where the cycle length is short, the diastolic pressure swell (presumably the reflected wave) may begin late in the diastolic period. If a new systolic upstroke coincides with the upswing of this swell, very high pulse pressure values can be obtained. This mechanism of augmentation by "superposition" was illustrated by pulses recorded from the system of man (108).

Aside from changes in pulse pressure and the form of the systolic peak, there are other aspects of pulse contour transformation which have no clear explanation. The pulse formed in the ascending aorta shows, after a variable but short period in which the pressure rise from the diastolic level is slow, a rather abrupt assumption of a steep and constant slope of pressure

rise. This anacrotic rise is maintained unchanged for at least 30 msec. It is then usually lost rather abruptly, often with a temporary interruption of pressure rise. This halt is called the shoulder of the pulse. The steeper the preceding slope, the more conspicuous is this shoulder. The rate of anacrotic pressure rise is clearly related to the amount of sympathetic stimulation of the left ventricle, which serves to speed the whole contractile process. Thus, with such stimulation, maximal outflow is reached earlier in systole, the shoulder tends to be at a relatively high pressure level, and the systolic peak of the pulse occurs earlier. A shortening of the length of the ejection period can be used as the basis of an assay method for sympathomimetic stimulation (100). With extreme cardiac stimulation, particularly when the stroke volume is reduced because of inadequate venous return, the shoulder may be so abrupt as to throw the whole aorta into vibrations. Under such circumstances, the height of the shoulder may be greater than that of any other part of the pulse, which makes the shoulder height represent the systolic pressure. In such cases, the pulse pressure may have higher values than would be anticipated from the stroke volume (94), in the peripheral vessels as well as in the ascending aorta.

The slope of pressure rise preceding the shoulder was found by Hamilton & Dow (42) to be propagated unchanged through the aorta. Alexander (4) showed some loss of steepness in the abdominal aorta, while I (99) found it to remain constant in the thoracic aorta and then to steepen in the abdominal aorta. The slope change is never marked, however, so that all three studies are compatible with the general conclusion that this first part of the pressure wave seems to move as an unchanged unit. All three also agree that the steep upstroke continues for a longer time interval the further from the heart the recording is made. This might lead one to the conclusion that this early part of the wave cannot be thought of as being propagated by repetitive accelerations of tiny segment volumes. It was pointed out earlier that the length of what is called a "small segment" of the aorta is undefined. The segment may have an appreciable length, and the volume contained, which is accelerated as a unit, have an appreciable mass. Thus it may be that the propagation of the first part of the pulse wave would involve fluid accelerations which would have many of the physical properties of a volume surge with inertia. If so, one would expect the "surge" to produce a progressively greater pressure rise in the lower regions of the aortic

funnel, where the distensibility is reduced. The speed at which the wave front would move would be dependent in part upon the force of the drive. For under these conditions, the ascending aorta would be "driving" the fluid through the various exit branches, one of which would be the thoracic aorta. These statements are similar to those made previously in the discussion of the relation between the pressure curve and the fluid displacement. It remains for future work to reconcile evidence which seems to favor the presence of a fluid surge with that which supports the proposed model, having wave propagation based on fluid displacement from one tiny vessel segment to the next.

A study of a great number of pulse forms leaves the impression that the volume uptake of the aorta in the period when the pressure shows this initial fast rise is not so large as would be expected from volume-pressure relations taken from a static stretch curve. This impression has not been proven. A rapid pressure rise at a time when the volume input is small was a pillar of the acceleration transient story of Peterson (90). One would like to explain an excess pressure height, if present, on the basis of wall hysteresis. If, in studies with rapid stretches of isolated vessels, there had ever been a considerable overflying of pressure at the end of a stretch, I would feel happier about this possible answer. If the impression is correct that pressure rise exceeds the expected volume gain, then it could also be true that in the interval of the shoulder of the pulse, the volume gain would continue, and thus "catch up" with the pressure.

When the pulse enters either the arm system or the aorta-leg system, the height of the shoulder is increased. In the human arm system, this elevation of the shoulder takes place largely in the subclavian arteries. The brachial pulse then shows two systolic waves, one representing the shoulder, and the other the later systolic part of the entering wave (12, 69, 108) (fig. 13). Very often the first is higher than the second, and hence sets the pulse pressure. This is particularly true when the anacrotic rise formed in the ascending aorta is steep and the shoulder is high. Late in a Valsalva maneuver, for example, the aortic pulse shows a steep anacrotic rise and high shoulder, but the rest of the pulse tends to collapse toward a low incisura. This contour is in keeping with the much reduced stroke volume. But in the brachial pulse the shoulder may remain at almost the normal height, which means that a pulse pressure measured from this height would have no relation to the stroke volume (108).

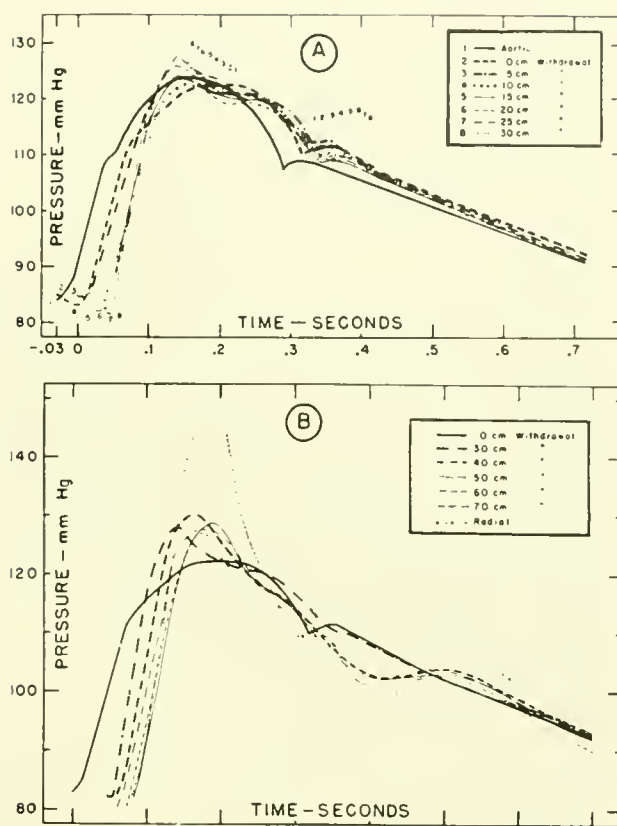


FIG. 13. Transformation of pulse in subclavian-arm system (subject 1). *A*: arterial pressure pulses recorded at 5-cm intervals during withdrawal of catheter through subclavian-upper brachial system of normal subject. Curve 1 is the aortic pulse, recorded from the thoracic aorta through a catheter inserted via right femoral artery. It has been set back by 0.03 sec. Curve 2 (starting at 0 time) is the pulse in most proximal point in subclavian artery reached by catheter inserted via left radial artery. *B*: continued withdrawal of catheter into lower brachial and radial system. Heavy solid line represents pulse from most proximal position in subclavian (0-cm withdrawal in *A*). The 30-cm withdrawal curve is last pulse from proximal unit (*A*), which still showed the simultaneous initial pressure peak. The 70-cm withdrawal is point at which catheter again entered needle in left radial artery. Pulse from right radial artery, recorded through a similar needle itself, is labeled "radial." [From Remington & Wood (108).]

Conversely, when the pressure is well supported in the upper aorta in late systole, the second wave of the brachial pulse becomes higher, and may then determine the pulse pressure. The maintenance of high, late systolic pressure in the upper aorta may be related to a large stroke volume. Hence in aortic regurgitation, where the ventricle is large and the total stroke volume much increased, the second wave of the brachial pulse becomes quite large. In the aortic pulse, the ejection interval is prolonged and

the systolic peak tends to come late. On the other hand, this maintenance of a high, late systolic pressure may also reflect a change in the acceptance by the aorta of ejected blood. For example, if the aortic pressure is acutely raised, the first result is a reduced stroke volume and a tendency toward shortening of the ejection period. This is presumably because the energy cost of ejection has been raised. As the heart size increases, the stroke volume shows some tendency to increase, and the duration of ejection becomes longer. The systolic peak comes later in systole. This pattern is clearest in animals with chronic hypertension. Part of this change may be due to a change in cardiodynamics (although not documented as such). A more likely explanation is that as the pressure rises, the front of the wave moves more rapidly through the whole receiving arterial reservoir, so that by midsystole the whole reservoir may be so nearly filled that the vessels act more as rigid conduits than as extensible tubes. As discussed previously, this tends to maintain the pressure at higher levels in the ascending aorta.

Conversely, when the aortic pressure is acutely lowered, the first few beats show a prolongation of systolic duration, with the systolic peak remaining in midsystole. After the first few beats, as the heart size becomes smaller, the stroke volume is reduced, and the peak tends to occur earlier (45, 94). At low pressures, the wave front moves so slowly through the reservoir that volume is still being readily accepted by the lower aorta, and hence by the ascending aorta, toward the end of systole.

The location of the systolic peak and the contour of the main part of the systolic portion of the pulse contour depend upon the varying characteristics of both the arterial reservoir and the cardiac ejection curve. This can also be taken to mean that the form of the ejection curve is molded by the rate of aortic acceptance of blood. Hence when the pressure is elevated, and the wave moves more rapidly through the vessels, the whole reservoir is filled in less time. Toward the end of systole, then, cardiac ejection need only compensate for the drainage loss, and the pressure can be held relatively high until ventricular relaxation begins (106). Conversely, when the aortic pressure is lowered and the pulse moves more slowly, the ejection of the same amount of blood will produce a greater rise in pressure in the upper aorta. If the pressure peak is still being propagated into the more distal vessels toward the end of systole, we would expect a fall in pressure in the ascending aorta, for the small amount of cardiac ejection could not

compensate for the fluid displacement required to construct the pulse wave.

The incisural vibration is formed in the ascending aorta and is propagated at an orderly rate not greatly different from that of the wave foot (98, 99). In many cases, and particularly when the systolic peak is reached late in the ejection period, it develops as soon as the ventricular pressure falls below the aortic level. In other cases, an appreciable pressure difference between ventricle and ascending aorta is developed before the notch appears. This is particularly true in pulses which have a high anacrotic shoulder and a collapsing pulse late in systole (98). Valve closure is also delayed when the aortic pressure is low. At times it may not appear until the isometric relaxation phase of the ventricle is almost complete (106).

It may be more than coincidence that the delay of the incisura is seen in those cases where the wave front is still moving through the reservoir. Valve closure must require a certain amount of flow reversal in the ascending aorta. It seems reasonable that this reversal could be accomplished more readily when outflow from the upper aorta is minimal (as with high pressure).

In most normotensive pulses the incisura has been damped out by the time the pulse enters the abdominal aorta. With elevated pressure, it may be seen as far as the femoral artery. With a lowered pressure level, it may be lost in the thoracic aorta. This difference is presumably attributable to the various visco-elastic properties of the wall at the different pressure levels. Whether the incisura is still present or not, the pulse of the lower aorta and the leg arteries shows a deep early diastolic trough. This is accentuated in fever, hyperthyroidism, and aortic regurgitation. Three different factors contribute to the presence and size of this trough. First, it is influenced by the late systolic fall in pressure of the central pulse. Second, the trough contains the remnant of the incisural vibration. Third, the trough appears to be set by the same mechanism that gives rise to the augmentation of the systolic peak, especially when this augmentation appears attributable to the achievement of resonance in the aortic system (2, 7, 99).

The fundamental form of the diastolic part of the pulse is probably the same for all pulses, no matter where recorded, except for the size of the periodic oscillations which are superimposed. Where such oscillations are minor, the slope appears exponential (140), but the relation of the rate of pressure fall to

existing pressure level does not remain constant during a prolonged diastolic period (25). It is difficult to generalize about the factors which contribute to the height of the diastolic oscillations. When the pressure is raised to hypertensive levels, the postincisural hump of the central pulse is usually much less conspicuous. This is due in part to the fact that it is then superimposed upon a part of the pressure curve which falls much more steeply, since the vessel distensibility is decreased in the high pressure range. It is much more probable that the relatively small size of the hump is a result of the fact that it starts near the time of the incisura (or even before), because the propagation velocity of the returning wave is more rapid. Conversely, at low aortic pressures, the postincisural hump of the central pulse may be quite conspicuous. This is partly because the basic diastolic slope is so shallow that any pressure increase is clearly evident, and partly because the frequency of the "resonant" oscillations is decreased, so that the swell comes later in diastole; also, it may be due partly to an actual augmentation of the swell itself.

Calculation of the Stroke Volume From the Central Pressure Pulse

On the theory that the aorta achieved immediate resonance, which means that the time interval between two successive pressure oscillations on all peripheral pulses would be the same and would be an index to the length and distensibility characteristics of the aortic reservoir, Frank (30) regrouped a formula similar to that of Bramwell and Hill to have it express the total distensibility of the whole resonant system. Hence where v is the pulse wave velocity, A the cross-sectional area of the bed, L its length, ρ the specific gravity of blood, and $\Delta P/\Delta V$ the slope characterizing the system distensibility:

$$v^2 = \frac{AL\Delta P}{\rho\Delta V} \quad (21)$$

With the simplifying assumption that $\Delta P/\Delta V$ remains constant throughout the range covered by a given pulse, we can, with extreme reservations, take ΔP to be the recorded pulse pressure, and ΔV the corresponding volume change. This assumes that the V for a given vessel would have a fixed relationship to the volume gain by the whole arterial bed. Rearrangement of the formula gives:

$$\Delta V = \frac{AL\Delta P}{\rho v^2}$$

Since the time interval between successive pressure peaks is assumed to be that required for the pulse wave to make a round trip through the system, $T = 2L/v$, or $L = Tv/2$. Substituting in the formula then gives:

$$\Delta V = \frac{ATv\Delta P}{2\rho v^2} = \frac{AT\Delta P}{2\rho v} \quad (22)$$

German workers have continued to use the Frank formula, or modifications of it. These formulas have received only restricted support in this country (124). While they may, perhaps, predict in reasonable degree the volume input into a rubber tube where the distensibility is uniform through the tube length, their use with the complicated arterial bed requires very large assumptions. First, there is the inference given above that the $\Delta P/\Delta V$ relation for any single vessel is indicative of the relation for the whole reservoir system. Second, A does not represent the area of any single vessel, but rather that of a hypothetical tube which happens to have the same dimensions as the mean of the whole reservoir network. Attempts have been made to take values for A from autopsy data, using the upper aorta, which certainly would not have the same dimensions as this mean. Further, autopsy data give a diameter at near zero pressure and not that at a physiological pressure. Third, since ΔV is the volume stored in the Windkessel during systole, it is not directly measurable. If a calculation is made for the drainage loss during systole (and various formulas have been proposed for calculating this loss), then the stored volume plus the calculated drainage loss would equal the stroke volume, which can be measured directly only under restricted conditions, but which is usually taken from a cardiac output determination. Fourth, L , the length of the reservoir network, cannot be directly measured. As described earlier, it has instead been calculated from the length of the resonant wave, as indicated by the time interval between successive pressure peaks of a peripheral pulse. This, of course, assumes that the reflecting end of the system is also the end of the Windkessel. The estimation of wave velocity and of the time interval between pressure peaks, by the techniques employed, leaves room for doubt as to the validity of any strict quantitation.

If the stroke volume could be directly measured, it might be that the various unknowns could be combined into a single constant. Its value, however, would apply only at the diastolic pressure for which it was derived, only if neither A nor L was subject

to physiological change, and only if a constant so derived for one individual could be applied to another. All these assumptions have seemed so precarious that the German formulas have not received favor in this country.

Yet the hope remains that some means can be devised by which the stroke volume can be predicted from the values of the pressure pulse. This would allow a quantitation of beat-to-beat changes, and also of the acute change in ejection volume that occur as the cardiovascular status is rapidly changed. We have no direct method applicable to closed-chest animals that can measure these stroke volume changes. Until we do, an indirect approach can serve a limited but useful purpose.

Another attempt at making this sort of indirect calculation was made by Bazett and co-workers (10). They divided the arterial reservoir into four parts: 1) the aortic arch and its large branches; 2) the whole of the descending aorta through the iliacs; 3) the subclavian-brachial systems; and 4) the femoral-leg system. They recognized that the pulse pressure would be different in these regions, and therefore concentrated instead on the pressure change taking place during diastole, when the previously stored blood was being discharged through the resistance vessels. They assumed that, by the time of the incisura, the whole arterial reservoir would be draining as a single unit, and that the pressure change could therefore be that from the level of the incisura of a central pulse to the end-diastolic value. Unfortunately, their central pressure pulses were rather inadequately recorded. Next, using calculations based on the size of the larger vessels of each arterial region as taken from autopsy data, and using assumptions and empirical adjustment of the derived diastolic volume values, they arrived at figures for the total diastolic volume for each region. The change in volume from this level was then equated as a function of the pulse wave velocity through the region, or

$$\Delta V = \Delta PK \left(\frac{V_1}{v_1^2} + \frac{V_2}{v_2^2} + \frac{V_3}{v_3^2} + \frac{V_4}{v_4^2} \right)$$

where ΔV is the total stored volume, the V 's are the calculated diastolic volumes of the four parts of the reservoir, and the v 's the respective wave velocities (which could be measured only rather crudely). With more modern technology, the basic data could be much more accurately recorded. The formula would still be rather cumbersome, and the necessary

measurements many. Two of the major weaknesses still present are that V cannot be directly obtained, any more than the A of Frank's equation can be, and that the v values of necessity must be taken from a single large artery in each of the regions. This assumes that this artery can fairly represent the whole system, and also that this velocity gives a true indication of vessel distensibility.

We presented another approach to the problem, worked out on the dog rather than on the human. For reasons which have been covered previously, we regarded the wave velocity as a most dubious measure of vessel distensibility. Instead, we substituted volume-pressure relations taken from data obtained by stretching isolated rings, and by injecting saline into occluded arteries of dead animals. We necessarily assumed that the values obtained would be practically the same for different animals. To make some correction for differences in body size, all values were expressed per square meter of body surface area. We also assumed that the transmission time through the various arterial beds would be the same for all animals, at the same diastolic pressure level. After making the studies described above, in which we calculated the presumed cardiac ejection curve on the basis of a summation of volume uptake values of the arterial regions taken serially as they were invaded by the pulse wave, as described above, we settled on the premise that such a summed total uptake, with a calculated systolic drainage added, should equal the stroke volume at the time of valve closure. Hence we could work with a single central pressure pulse, laying back the transmission time to each of the four major divisions of the arterial bed, from the incisura. The pulse pressure to be quantitated for each bed would then simply be the pressure shown at this interval before valve closure. In other words, the point at which this time interval intercepts the pressure pulse curve indicates the pressure developed in the bed in question at the end of systole. This assumes that there was no change in pulse contour during propagation. More rightly, it assumes that any contour change present during propagation would be constructed by a redistribution of the volume of blood ejected into the ascending aorta to create the given central pressure pulse. Attempted modifications based on actual pulse contours taken at various points in the aorta did not alter the value of the calculated stroke volume to significant degree.

Without introducing any empirical correction factor, the agreement between the predicted and

the stroke volume derived from the dye injection or Fick's procedure was within 12 per cent (44). Further work brought to light two areas of discrepancies. First, the predictions tended to underestimate the actual stroke volumes at high pressure ranges. The volume-pressure values were then empirically adjusted to take care of this (94). The correction used is almost identical to the difference between the single continuous stretch curve of figure 3 and the curve connecting the midpoints of the consecutive loops, which fact suggests that there may be a theoretical foundation for the empirical correction. The second and more serious failure of the method is that it yields a definite overestimation of the actual stroke volume in some shock states in which the pressure shows a brisk anacrotic rise with a high shoulder, but is then poorly sustained later in systole. This type of pulse has been described above. The possible causes of the failure in prediction for these rare pulses were discussed rather fully in a symposium presented in 1952 (86a) and little more light has been shed on the problem since.

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Pulsatile blood flow in the vascular system

MERRILL P. SPENCER
ADAM B. DENISON, JR.

*Department of Physiology and Pharmacology, Bowman Gray
School of Medicine, Winston-Salem, North Carolina*

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THE HIGHLY PULSATILE NATURE of the blood flow in both the systemic and pulmonary circuits primarily arises from the intermittent action of the heart as a pump. Each ventricle has a valve at its exit and entrance such that the blood flow and velocity oscillate from near zero, when the valves are closed, to relatively great values during the time when the valves are open. Great changes in the velocity arise from the starting and stopping of the blood stream with the opening and closure of these valves. Secondary causes of flow pulsations, particularly in the veins, arise from the respiratory fluctuations and muscular contractions.

I. METHODS OF MEASUREMENT

Methods for the detection of blood flow and pressure oscillations within this system require a frequency response flat to at least 100 cps and without phase shift. Present day pressure systems achieve this ideal quite well if one does not introduce long elastic catheters between the pressure tap and the transducer. Present day blood flowmeters, however, have not achieved this degree of perfection, but recently great progress has been made. In addition to the frequency and phase characteristics mentioned, a blood flowmeter should be capable of detecting the blood flow or

velocity from either the surface of a surgically exposed vessel or by means of a catheter tip introduced into the flow stream, but without causing significant distortion of the flow dynamics.

All the blood flow recordings gathered by the authors for this chapter, if not otherwise indicated, have been made with a 240-cycle square-wave electromagnetic flowmeter (11) introduced in 1953 as the first practical instrument for measuring blood flow in any of the body's arteries and veins which have been surgically exposed. As used here, this instrument has a flat frequency response to 40 cps, and is down by 50 per cent at 100 cps, and, although the principle is capable of an infinite frequency response, these limitations are necessary in a practical instrument primarily because of the carrier frequency residual which would otherwise appear on the flow record. The magnetic probes applied to the blood vessels restrict pulsations and encroach on the lumen to the extent of reduction in cross-sectional area by approximately 5 to 10 per cent. Such slight constriction assures firm contact of the electrodes to the arterial wall. Experimental testing showed that this amount of constriction caused no perceptible change in the recorded flow pulse (45).

Properties and Principles of Flowmeters

For recording of vascular flow velocity pulses an ideal flowmeter should possess several properties: a linear response to forward and backward flows, a stable zero reference, and a frequency response adequate to follow the phasic phenomena being recorded. It should also be unaffected by nonrelated phenomena such as blood pressure, internal noise, and muscle action potentials. Furthermore, its operation should not modify the phasic flow patterns, mean flows, or blood pressure. To meet this last requirement completely would mean that not only must the blood vessel under consideration be unobstructed and non-cannulated, but also that the recording be done without anticoagulants or anesthesia and without psychic trauma to the experimental subject (59).

Obviously, a practical flow-recording system requires some compromise with the above ideals; also, such an elegant device would not be necessary for most research work. If one knows the general character of the quantities to be recorded, he may use with confidence an equipment the characteristics of which are considerably more restricted than the ideal. For instance, a frequency response of zero to 50 cps is felt to be adequate for cardiovascular work (6, 46); also,

when recording ascending aorta flow, zero drift is not serious since the flow can be taken to be zero at the end of diastole, thus giving a continuously repeated zero check. Therefore, an instrument used for cardiac output measurements may have considerable drift of zero and still be satisfactory for the purpose if it meets the other requirements, although it might be unsatisfactory for other situations where a stable zero reference is essential (14).

Many different principles have been used for flow recording; all have inherent potentialities for errors in application or interpretation. These principles and the instruments which embody them are discussed in detail in Chapter 38. Here it will be necessary only to list the different types of instrument and certain references to the literature which are not found elsewhere either in this chapter or in Chapter 38.

a) Electromagnetic flowmeters (1, 3, 5, 8, 9, 16, 24, 53, 57, 63). b) Ultrasonic flowmeters (25). c) Nuclear magnetic resonance (4, 23). d) Pendulum or bristle flowmeters. e) Catheter tip pickups (36, 38). f) Turbinometers (40, 41). g) Differential pressure flowmeters (10, 17, 39).

Cognate Phenomena

LATERAL AND DIFFERENTIAL PRESSURES. In any critical study of the relationship of the dynamics of pulsatile flow it is necessary that pressure and flow be measured simultaneously, and that the pressure be picked up from a pressure tap the orifice perimeter of which is in a plane parallel to the flow stream. One highly practical system is to use a "clip needle" which by means of a flexible clip holds the end of the needle against the inside of the blood vessel wall (49). If a Huber point is used on the clip needle, the recorded pressure can be a true lateral pressure.

The use of differential pressure measurements has greatly enhanced our interpretation of the phenomena occurring simultaneously within the vascular system. Such a method usually takes the form of two pressure taps conducted separately to either a differential pressure transducer or to two individual pressure transducers the amplified signals of which are electrically subtracted from one another continuously. The latter system has the advantage of being able to view the individual pressures which make up the differential pressure recording. These individual recordings are useful in identifying artifacts which may arise.

COMPUTER TECHNIQUES. For a proper understanding of the hemodynamics of the cardiovascular system, a full

appreciation should be had for the relationship between flow velocity, volume, and displacement. These relationships may be expressed best by means of calculus symbology, as follows:

$$\begin{aligned}\text{Displacement (cm)} &= \int_0^t \text{Velocity (cm/sec)} dt \\ \text{Velocity (cm/sec)} &= \int_0^t \text{Acceleration (cm/sec}^2\text{), } dt \text{ and} \\ \text{Volume (cm}^3\text{)} &= \int_0^t \text{Flow (cm}^3\text{/sec)} dt \\ \text{Flow (cm}^3\text{/sec)} &= \int_0^t \text{Volume acceleration (cm}^3\text{/sec}^2\text{)} dt\end{aligned}$$

For example, the cardiometer tracings during the systolic ejection period may be said to be the negative integral of flow through the aortic and pulmonary valves, and the diastolic cardiometer tracing is the integral of the flow through the A-V valves. Also, the radial displacement of the arteries and veins may be said to be the integral of the radial velocity of blood flow within the lumen.

Analogue computer techniques, useful in the study of vascular hemodynamics (50), allow one to move from volume to flow to acceleration by means of integration, or the reverse, through differentiation. Two types of integration are currently in use: 1) the true time integral which is an instantaneous sum of a given function, beginning from any given time; and 2) damping or "meaning," an older usage of the word which implies a mean value of a periodic function. Damping may be accomplished either mechanically or electrically. The most practical way to perform this mechanically in a pressure recording system is to introduce compliance or resistance into the transmitting system, e.g., by means of a bubble in the gauge or a partial occlusion clamp on the catheter tubing. Damping in an electrical system amounts to a fully charged integrating circuit in which the rate of current inflow into the integrator over one pulse cycle equals the rate of current outflow.

II. ELEMENTS OF VASCULAR HYDRAULICS

The arterial system is a many-branched elastic conduit for distribution of blood from the heart to all body tissues. The caliber ranges from 35 mm for the human aorta to 7 μ for the capillaries. Over this wide range each vascular segment may be described by three fundamental physical properties: resistance, inertance, and compliance.

Resistance (R)

This arises from the friction between shearing molecules flowing through the segment. Expressed in terms of the pressure difference (15) across the resistance, ΔP_R , in dynes per square centimeter¹; the blood velocity, u , in centimeters per second; the cross-sectional area, A , in square centimeters; and the flow ($F_R = uA$), in cubic centimeters per second,

$$R = \frac{\Delta P_R}{u \cdot A} = \frac{\Delta P_R}{F_R} \quad (1)$$

After Poiseuille, in terms of vessel dimensions, length (l) in centimeters, radius (r) in centimeters, and blood viscosity (η) in dynes · second per square centimeter,

$$R = \frac{8\eta l}{\pi r^4} \quad (2)$$

The vessel wall also has a small resistance opposing radial distention and collapse. The inverse of resistance or conductance ($1/R$) is often a useful term. The symbol for hydraulic and viscous resistance is taken from electronics (WW).

Inertance (L)

This resides primarily as the mass of blood and secondarily as the mass of the arterial wall. It is expressed in terms of acceleration (a), and attendant pressure difference across the inertance, ΔP_L , in dynes per square centimeter.

$$L = \frac{\Delta P_L}{a \cdot A} = \frac{\Delta P_L}{dF_L/dt} \quad (3)$$

where F_L is the flow through the inertance, and where $L = m/A^2$, m is the mass of the blood in the segment of artery under consideration expressed in grams, and A is the cross-sectional area in square centimeters. In terms of vessel dimensions (55), l and r , in centimeters and blood density (ρ_B) in grams per cubic centimeter,

$$L = \frac{\rho_B l}{\pi r^2} \quad (4)$$

¹ Pressure in dynes per square centimeter should be used instead of the conventional pressure in millimeters of mercury. The following expression is used to convert from millimeters of mercury (h) to pressure in dynes per square centimeter (P):

$$P = 0.1 \text{ g } \rho_{Hg} h = 1323 \times \text{mm Hg}$$

where g is the acceleration of gravity in cm/sec², and ρ_{Hg} is the

The symbol for inductance is that for electrical inductance ($\text{---}\text{---}\text{---}$). Because inductance is defined in terms of volumetric acceleration, the larger the cross section of the vessel lumen, the smaller is the inductance in a vessel of given length.

Compliance (C)

Compliance is a property of the arterial wall arising from its distensibility and chiefly residing in the elastic fibers. The contribution of smooth muscle and fibrous tissue has not been determined. It is expressed in terms of blood volume (V) in the segment and the attending pressure difference across the vascular wall ΔP_c .

$$C = \frac{V}{\Delta P_c} = \frac{1}{\Delta P_c} \int F_c dt \quad (5)$$

where F_c is the flow into the compliance, or in terms of dimensions (22) length (l), radius (r), wall thickness (o), and the modulus of elasticity (E):

$$C = \frac{2\pi r^3}{Eo \cdot l} \quad (6)$$

The symbol for compliance is that of electrical capacitance ($\text{---}\text{---}\text{---}$).

Axial Flow

In a segment of rigid pipe axial flow is analogous to the current in the diagram of figure 1. Where $\Delta P_{\text{axial}} = P_1 - P_2$, ΔP_a at any instant in time will be equal to the sum of the pressure differences due to the R and L components. Thus:

$$\Delta P_{\text{axial}} = \Delta P_{\text{Resistance}} + \Delta P_{\text{Inductance}} \quad (7)$$

(Any pressure gradient resulting from gravity cancels if the pressures are referred to the same level.) Substituting from equations 1 and 3, and considering $F_R = F_L = F$,

$$\Delta P_o = RF + L \frac{dF}{dt} \quad (8)$$

integrating with respect to time we have

$$F = \frac{1}{L} \int (\Delta P_o - RF) dt \quad (9)$$

This equation may be solved continuously by an analogue computer and has some practical applica-

density of mercury at the existing experimental conditions in g/cm³.

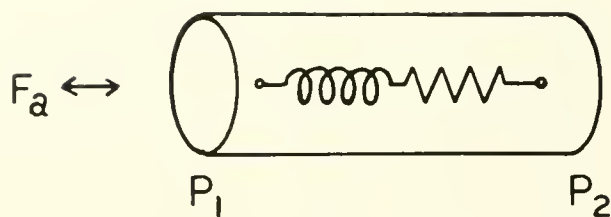


FIG. 1. Electrical analogue of axial flow and pressure in a rigid tube.

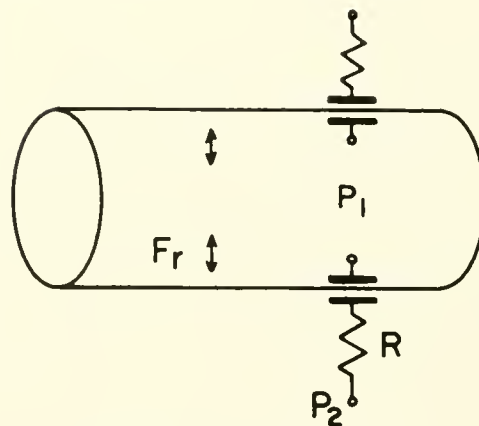


FIG. 2. Electrical analogue of radial flow in an elastic tube.

tion in the ascending aorta (12, 13). The procedure is to subtract P_2 from P_1 to obtain ΔP , and then to subtract RF from ΔP and integrate the result. If $1/L$ is known or is chosen arbitrarily, R may then be adjusted until F achieves some known boundary condition such as $F = 0$ during diastole. Figure 3B graphically illustrates the procedure. If accurate values for vessel dimensions, blood density, and viscosity are available to calculate L and R , the result can be obtained in terms of actual flow in cubic centimeters per second, otherwise the answer only yields the velocity in centimeters per second.

Radial Flow

In a visco-elastic artery, radial flow is analogous to the current in the diagram of figure 2.

$$\Delta P_{\text{radial}} = \Delta P_c + \Delta P_R \quad (10)$$

where ΔP_{radial} represents the pressure difference across the arterial wall ($P_{r1} - P_{r2}$). Substituting from equations 1 and 5, where $F_r = F_c = F_R$,

$$\Delta P_r = \frac{1}{C} \int F dt + RF \quad (11)$$

and differentiating,

$$F = C \left[\frac{d\Delta P_r}{dt} - R \frac{dF}{dt} \right] \quad (12)$$

or rearranging equation 11

$$F = \frac{1}{R} \left[\Delta P_r - \frac{1}{C} \int F dt \right] \quad (13)$$

Since measurements of pressure and vessel diameter are very similar, friction within the arterial wall and radial inertance are apparently quite small, although in the final analysis, as clearly indicated by Peterson (35), one must consider acceleration along with distensibility and friction.

When the total flow (F_T) in an elastic pipe is considered, both radial and axial flow equations must be combined as follows for instantaneous flow: $F_T = F_{axial} + F_{radial}$, and, from equations 9 and 12,

$$F_T = \frac{1}{L} \int (\Delta P_o - R_o F_o) dt + C \left[\frac{dP_r}{dt} - R_r \frac{dF_r}{dt} \right] \quad (14)$$

In analogue computer language this equation is solved as in figure 3. Patel *et al.* (33) have found negligible degrees of inertance and resistance in the pulmonary artery wall.

A more complete hydraulic diagram of an arterial segment may be well shown as in figure 4. L_1 , R_1 , and C_1 represent its most important elements, with R_2 and R_3 representing radial and axial resistance, and C_2 representing axial compliance. The complete arterial system may be viewed as a continuous linkage of such segments, each branch and segment having quantitative differences in magnitude of the individual physical elements. At the same time, the physical elements of any segment or group of segments may be described by over-all "lumping" of the elements.

The arterial system is not a passive network because the elements may be influenced by the nervous system, endocrine system, metabolic processes in the wall, and changes in the physical properties of the blood. In addition, the values of the elements are nonlinear functions of pressure, vascular dimensions, velocity profile and many other influences. In spite of these complications, much can be learned by linear analysis of the pressure and flow pulses at various

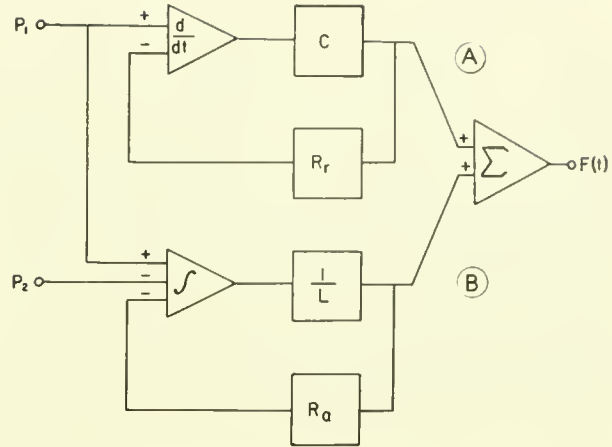


FIG. 3. Analogue computer diagram for solution of the equation of liquid flow in an elastic tube. P_1 and P_2 represent the lateral pressures from two stream points. ΔP is the independent variable ($\Delta P = P_1 - P_2$).

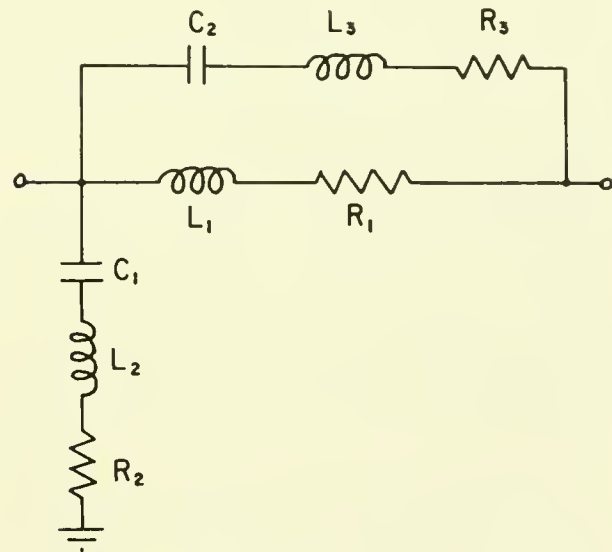


FIG. 4. Elaborate electrical analogy of a vascular segment.

points within the arterial network studied under reasonably steady-state conditions.

Hydraulic Impedance

This is the concept of total opposition to pulsating and constant flow. Drawing on the electrical symbolism, we have Z , X_L , X_C , and X_R , where Z represents the total impedance, and X_L , X_C , and X_R equal the inertial, compliant, and resistive impedances. X_R is the opposition to flow, X_L is the opposition to change in flow, and X_C is the opposition to change in volume. Both

X_L and X_C depend on the frequency (ν) as follows:

$$X_L = 2\pi\nu L \quad X_C = \frac{1}{2\pi\nu C}$$

The impedance to blood flow through L and C elements will therefore be expected to be frequency dependent, and may be termed hydraulic reactance in contradistinction to resistance which is not frequency dependent. Hydraulic impedance may be expressed as dP/dF , i.e., the rate of change of pressure with respect to simultaneous rate of change of flow. On a pressure-flow diagram, impedance would be represented by the tangent to the curve at any given time.

Flow Source Versus Pressure Source

The impedance or "stiffness" of the flow source and pressure source may be expected to influence the response of a vascular segment. For example, a small branch, such as a renal artery arising directly from the aorta, is fed by a stiff pressure source, inasmuch as great changes in renal vascular impedance encountered within extreme physiological ranges have no effect on the abdominal aorta pressure.

On the other hand, the left ventricle without external controls behaves as a flow source because relatively great changes in systemic arterial impedances (viz., aortic stenosis, hypertension, vasodilation) cause small changes in the cardiac output. On a beat-to-beat basis, therefore, the left ventricle may be considered to be a stiff flow source or volume pump, and the response of the arterial system is greatly influenced by this fact. The performance of the left ventricle as a volume pump is illustrated in figure 5. The carotid sinus feedback loop tends to make the heart rate and strength of contraction vary inversely with the arterial pressure, but requires several beats for its correcting action. Hormonal negative feedback loops also act on the heart to cause it to perform as a stiff pressure source, but act even more slowly than the reflexes.

The Analogy Approach

This is: *a*) to diagram an electrical network model of specific segments of the arterial system based on qualitative facts available from physiology by identifying blood pressure and blood flow with electrical voltage and current; *b*) to test the model against conditions in an experimental animal by pulsing a direct analogue or an analogue computer with electrical voltage or current transduced from the

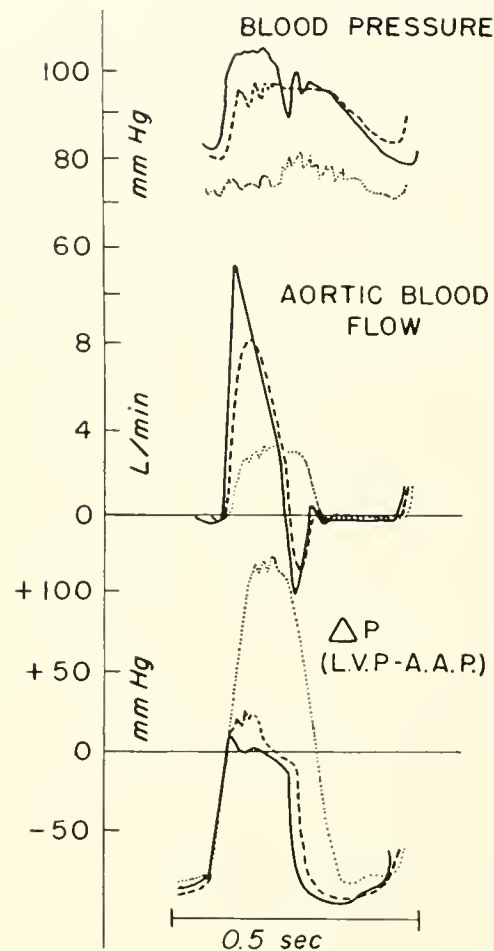


FIG. 5. Response of the dog's left ventricle to sudden increase in outflow resistance caused by partial occlusion of the ascending aorta. — Control; ---- moderate obstruction; severe obstruction.

blood pressure or flow. The computer is programmed to solve the equation of the electrical network, but in this case in terms of pressure and flow instead of voltage and current. Several general considerations of the analogue approach are available (32, 34, 54, 60).

Considerations of this section approach the vascular system from the standpoint of a transient response as distinguished from the usual use of steady-state oscillation in which the harmonic content must be known to reach a solution (20, 26, 51, 61, 62). The transient response method has the advantage of giving an instantaneous solution while in addition each term of the equation has physiological meaning. To regard the arterial pulse as a steady-state oscillation is to fail to recognize the input pulse and the response of the vessels as two independent phenomena

and overemphasize the regularity of the heart rate. Also, the terms of a series such as the Fourier have no real physiologic meaning and in fact may fail to show a dominant and important frequency such as the arterial resonant wave.

III. SYSTEMIC ARTERIAL FLOW

Shipley *et al.* (44) and Pritchard *et al.* (37) made one of the most comprehensive recordings of the arterial flow pulses using the differential pressure flowmeter. They offered no fundamental theory to explain the recorded phasic pressure-flow relationship. Although some exception may be taken to their flowmeter, the general form of the flow pulses agrees well with more recent electromagnetic noncannulating recordings.

Blood Flow in the Ascending Aorta

The arterial network is pulsed by a flow pulse from the left ventricle normally of the configuration in figure 6. This recording is taken with the square-wave electromagnetic flowmeter on the ascending aorta, 3 to 5 cm distal to the aortic valve. What were apparently the first accurate phasic recordings were made by Wetterer (58). The linear acceleration of the blood by the left ventricle is remarkable, reaching greater than 8000 cm per sec per sec in an anesthetized open-chest dog (47). At the end of acceleration, the velocity of the blood in the ascending aorta may easily exceed 100 cm per sec in the resting state. Deceleration takes place at a rate approximately one-sixth of acceleration until closure of the aortic valve when a sharp notch of deceleration and acceleration brings the flow to nearly zero for the duration of diastole.

For many practical purposes this flat "uneventful" tracing during diastole in the ascending aorta may be used as a zero flow reference to compute the stroke volume. The fact that coronary flow is not included may produce a small unknown error. Apparently, the diastolic flow curve in the ascending aorta is flat at nearly zero because the reversing effect of coronary flow is balanced by the forward effect of decompression of the first portion of the ascending aorta. The left ventricular ejection velocity at the root of the aorta recorded by Pieper (fig. 7) is similar to the flow pulse throughout the ascending aorta. Since this instrument records the axial velocity, it appears that the velocity profile of the ascending aorta is relatively

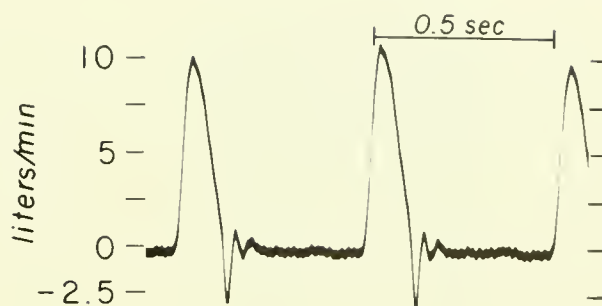


FIG. 6. Flow pulses in the ascending aorta of an unanesthetized dog. C-core electromagnetic probe was implanted 6 weeks prior to this record on the ascending aorta. Electrical connections were made by means of implanted subcutaneous wires, brought to the surface through a small superficial incision.

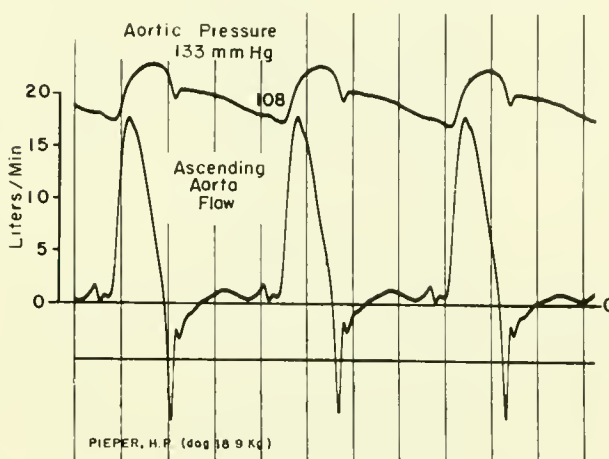


FIG. 7. Axial flow pulse in the ascending aorta recorded by means of velocity probe situated in midstream. [From Pieper (36).]

flat. More backflow occurs here during early diastole presumably because of diastolic coronary flow.

The effect of exercise on the ventricular ejection pulse is illustrated by a remarkable experiment by Olmsted (personal communication), figure 8. The animal had a magnetic probe implanted on the ascending aorta and an arrangement for remote pressure recording. After one month's recovery from the surgical procedure he was exercised by running in a harness behind a station wagon carrying recording equipment. Suitable wiring carried the electrical signals between the automobile and the dog. The course was one-half mile over rough terrain at an average speed of 10 mph. Upon standing, the cardiac output increased primarily because of increased heart rate without change in stroke volume and with little change in form of the ejection pulse. Running at 5 mph increased cardiac output by increasing both

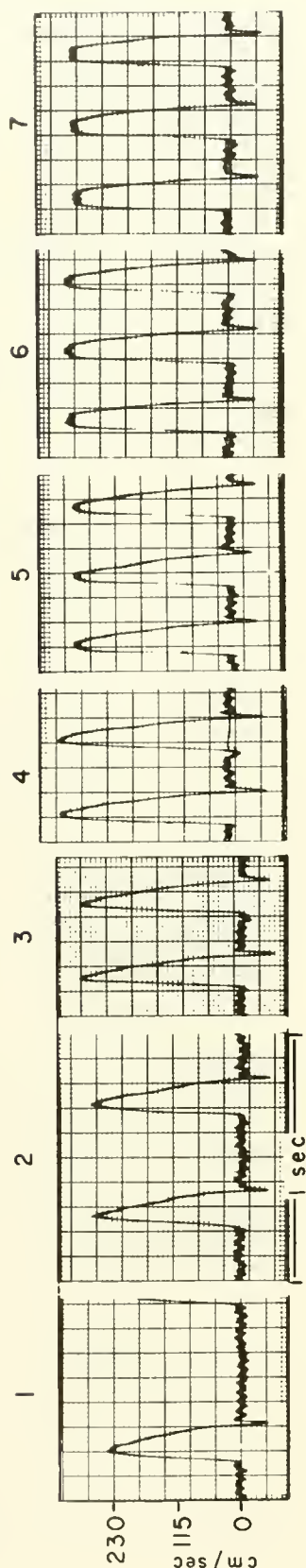


FIG. 8. Effect of exercise on blood flow in the ascending aorta of a trained dog. See table 1 and text. (From Olmsted, personal communication.)
1 = lying, 2 = standing, 3 = 5 mph, 4 = 8 mph, 5 = 10 mph, 6 = hill, 7 = $\frac{1}{2}$ mile point.

TABLE 1. *Ascending Aorta Flow During Exercise*

| Exercise | Elapsed Time, Sec | Cardiac Output Liter/min | Blood Pressure (Arch) | Stroke Volume, ml | Heart Rate/min |
|-----------------|-------------------|--------------------------|-----------------------|-------------------|----------------|
| Lying | 0 | 2.9 | 139/86 | 25 | 113 |
| Standing | 0 | 3.5 | 122/73 | 25 | 140 |
| 5 mph | 18 | 5.6 | 86 | 28 | 200 |
| 8 mph | 25 | 6.2 | 81 | 31 | 200 |
| 10 mph | 55 | 6.0 | 79 | 28 | 214 |
| Hill (5% grade) | 120 | 7.5 | 92 | 35* | 214 |
| Half mile | 180 | 6.6 | 98 | 33 | 200 |

* 40% above control.

heart rate and stroke volume. Further effort increased output primarily by increasing the stroke volume with little change in heart rate. The increase in stroke volume was evidenced by a change in the contour of the ejection pulse from its normal triangular shape toward that of a square wave. The failure to increase greatly the peak velocity may have been due to turbulence impedance or to a limit in the rate of ventricular contraction. As a result of the limiting factor on peak velocity, the animal may have been near his maximum cardiac output. Table 1 gives the flow and pressure values for figure 8.

Pressure-Flow Relationship in the Ascending Aorta

Figure 9 illustrates the instantaneous pressure difference (ΔP) along 3 cm of the ascending aorta with the axial flow through the same segment. ΔP deflections lead the flow deflections by approximately 90 degrees, which suggests that mass-acceleration laws dominate. A very close approximation of actual flow may be computed from ΔP using equations 5 and 9. In this situation radial flow is small compared to axial flow, thus absence of the radial flow term seems unimportant especially when only the net axial flow is desired.

Fry (13) originally pointed out this relationship and its practical use in a catheter-tip flowmeter. Assuming that the flow profile in the ascending aorta is flat, one would theoretically need only the cross-sectional area of the ascending aorta to compute cardiac output from the pressure gradient. The application of this principle using a double lumen catheter is at the moment fraught with many practical difficulties, primarily concerning Pitot effects at the catheter tip and accurate measurement of the lumen cross section.

Ventricular Ejection Gradients

Because of mass-acceleration effects, ventricular ejection during the deceleration phases takes place against

the pressure gradient (47). Figure 10 demonstrates this fact at the aortic valve where, during late systole blood is flowing through the valve against a pressure gradient. A similar finding has been shown for the right ventricle (H. Okino, unpublished work). These findings prove dynamically that the forward resistance of the aortic and pulmonary valves is slight. Further, the energy of external work of the ventricles is spent in raising the blood pressure to sufficient level to accelerate the blood into the aorta and pulmonary artery.

Windkessel Model of the Arterial System

This has been a concept of limited usefulness to explain the form of the arterial pulses. It may be represented by the analogue of figure 11. The arterial chamber is represented by the compliance (C), and the peripheral resistance by the resistance term (R). The basic relationship here, between pressure and

flow, is $F = C(dP/dt) + (1/R)P$. When this electrical model is experimentally pulsed by a current transduced from the flow in the ascending aorta (F), the voltage form (P) is obtained. By comparison, the actual pressure pulse in the aortic arch (P) deviates in several details from P : 1) P has a superimposed 3 to 6 cps oscillation apparent from midsystole throughout diastole, and 2) P has a more prominent "incisura" marking aortic valve closure and a more abrupt rise, often with an anacrotic wave. In addition, the windkessel model fails to explain the changes in form occurring along the arterial network. Detail 2 appears if the analogy is elaborated by the placement of some restraint on the distensible element, i.e., taking into consideration the friction in lateral expansion of the arterial wall, as in equations 12 and 13. Detail 1 requires a concept of reflections or resonant network filter as explained in the succeeding paragraphs. Cope (7) has attempted new use of the windkessel concept using empirical constants.

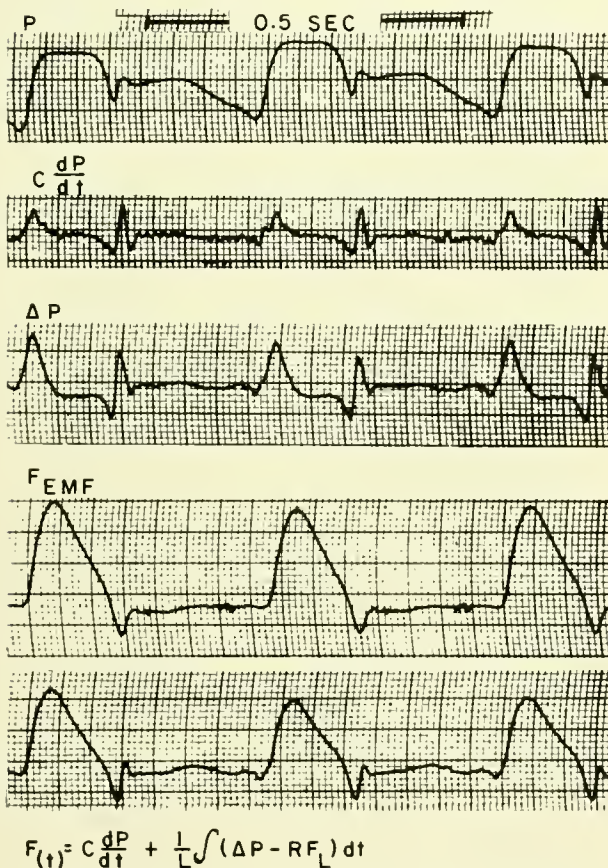


FIG. 9. Computer solution to blood flow in the ascending aorta using the analogue computer of fig. 3. F_{emf} = the flow measured by the electromagnetic flowmeter. F_t = computed flow. $C(dP/dt)$ = the radial flow pattern derived from the time differential of the aortic arch pressure P .

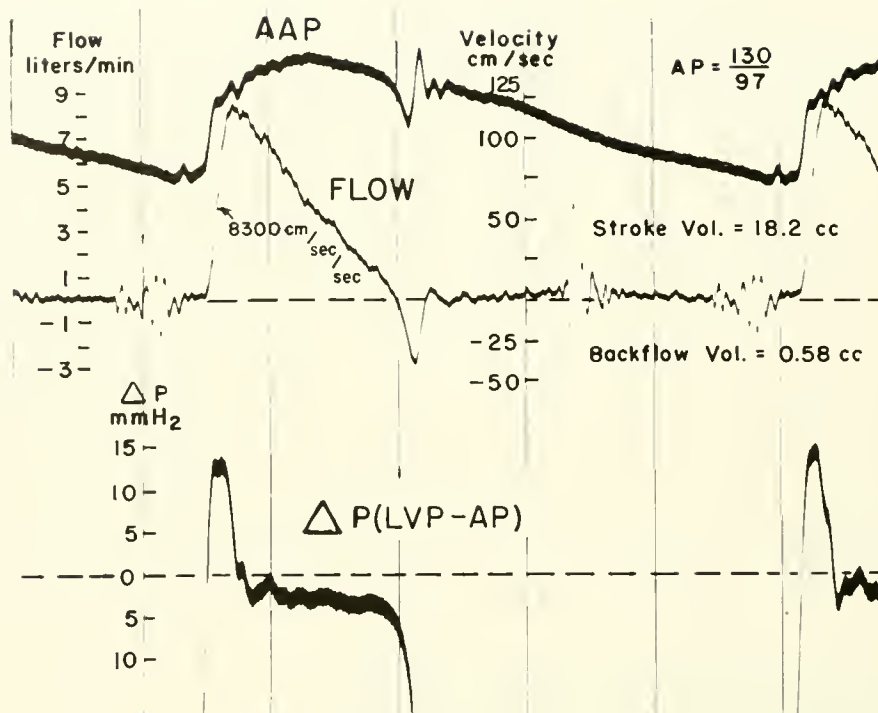
Aortic Transformation of Flow and Pressure Pulses

Figure 12 illustrates the changes in form and magnitude of the flow pulses between the ascending aorta and the abdominal aorta. The flow in the descending thoracic aorta represents an intermediary form and well illustrates the superimposition of a prominent smooth 3 to 6 cps wave decreasing in amplitude throughout diastole. This wave referred to as the "resonant" wave frequently causes backflow in diastole throughout the aorta and many of its branches. Considered as a whole, the arterial system is a low-pass filtered hydraulic supply, i.e., it is designed to offer negligible impedance to steady flow and frequencies up to 10 cps. There is normally one frequency between 3 and 6 cps to which it offers lowest impedance, and resonates at that frequency with each beat of the heart. Early physiological workers recognized this resonant system as analogous to a low-frequency underdamped manometer system.

Resonant-Network Model of the Arterial System

This represents an improved concept to explain the transformation of arterial pressures and flow pulses. It is diagramed in figure 13. C_1 roughly represents the lumped compliance of the aortic arch and its branches, and C_2 , the lumped compliance of the abdominal aorta and its branches. L represents the lumped inertance of the blood in the descending aorta. F_H represents the forcing function of the left

FIG. 10. Relationship between the differential pressure and flow through the normal aortic valve. The ordinates refer to the tops of these simultaneous tracings. ΔP = left ventricular pressure (LVP) minus ascending aorta pressure (AAP). The pressure gradient is against the direction of flow in the latter part of systole.



ventricular ejection pulse. R_1 and R_2 represent peripheral resistances which may be adjusted relative to C_1 and C_2 to give any desired ratio of pulse pressure to mean pressure at P_1 .

C_1 , C_2 , and L form a series resonant circuit and may be adjusted to give any resonant frequency, and R_3 and R_4 are chosen to provide the proper damping ratio of the observed resonant wave in the arterial system, as well as the high frequency details. When C_2 is smaller than C_1 , the P_2 pulse pressure is greater than P_1 pulse pressure, thus explaining a time-honored observation that the arterial pressure in the legs rises higher than in the arms during systole.

Figure 14 demonstrates the degree of accuracy with which such a grossly lumped electronic model may reproduce the observed set of pressure and flow values in the arterial network. The resonant-network model embodies several concepts which provide a rational explanation of the major hydraulic features of the arterial system.

1) The over-all frequency response characteristics of the arterial system may be taken as that of an analogous filter network (56), figure 15.

2) The resonant frequency (ν_n) varies from 2 to 10 cps and is increased by hypertension produced by increased cardiac output and sympathetic constrictor agents. It is also increased in cardiac failure due to mitral stenosis. Hypotension from decreased

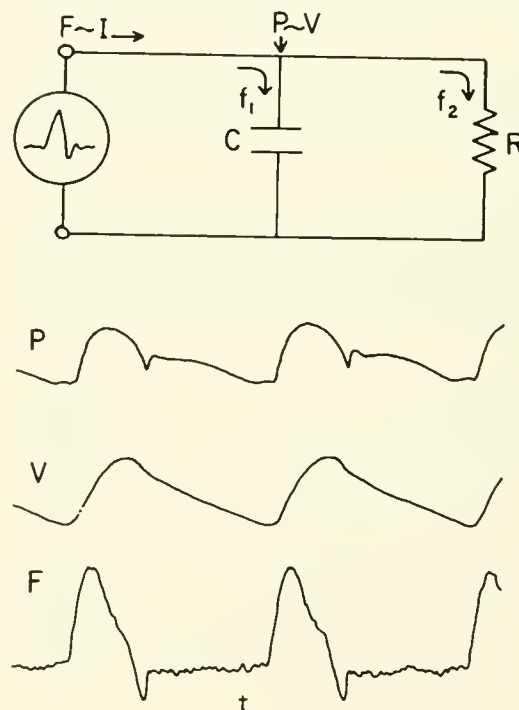


FIG. 11. Electrical analogue of the windkessel model of the arterial system with experimental testing. P represents the pressure in the aortic arch. V represents the voltage across the parallel resistor and condenser. F represents the measured blood flow in the ascending aorta and the electrical input current forcing the analogy.

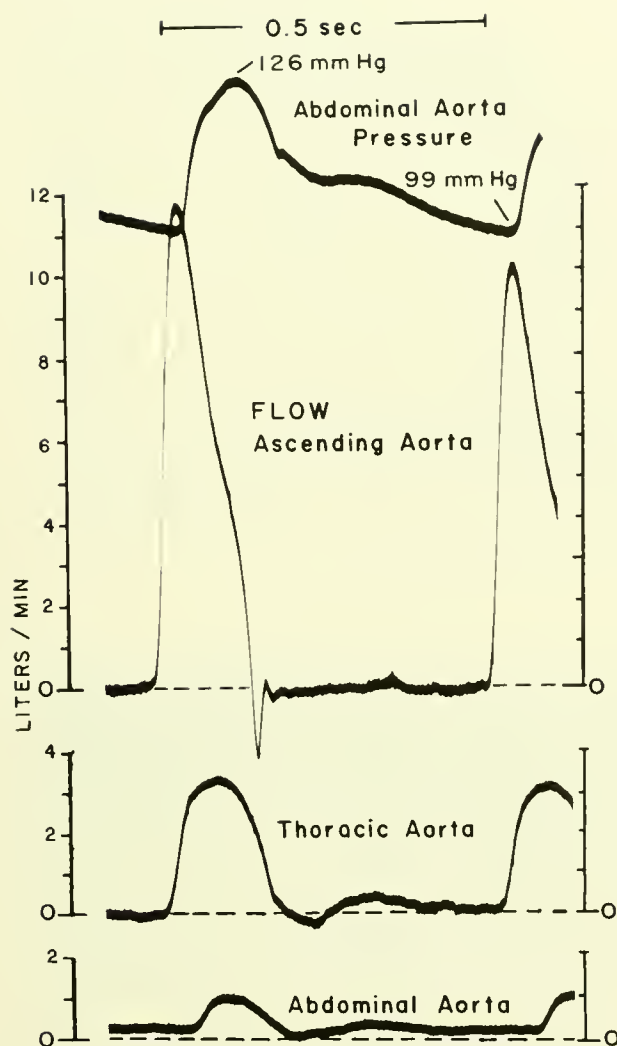


FIG. 12. Transformation of the aortic blood flow between the ascending aorta and abdominal aorta. High frequencies are attenuated and a resonant frequency is superimposed.

cardiac output decreases the resonant frequency. Presumably the over-all compliance changes more than the inertance in these conditions.

3) The amplitude of the resonant wave is increased when, in tachycardia, the systolic flow pulse is in phase (48) with the resonant wave.

4) The pressures and movements in the arterial system represent, at any steady state of the hormonal and nervous controlling conditions, transient responses to the flow input from the left ventricle.

5) The augmentation of the pressure pulse, as it is transmitted to the abdominal aorta, results from the lower gross compliance of the abdominal arterial bed as compared to the aortic arch vascular bed.

TABLE 2. *Distribution of Arterial Flow Pulse*

| Artery | Circumference, cm | Mean Peak Flow, ml/min | Mean Peak Velocity | |
|---------------------------|-------------------|------------------------|--------------------|--------|
| | | | cm/min | cm/sec |
| Ascending aorta | 6.28 | 11,870 | 3,780 | 63 |
| Descending thoracic aorta | 5.0 | 3,243 | 1,621.5 | 27 |
| Abdominal aorta | 3.4 | 1,108 | 1,256.2 | 21 |
| Iliac | 1.8 | 750 | 1,429 | 23 |
| Femoral | 0.7 | 182 | 3,275 | 54.6 |
| Renal | 1.4 | 176 | 2,045 | 34.1 |
| Carotid | 1.5 | 193 | 1,401 | 23.4 |
| Brachial | 0.7 | 94 | 1,162 | 19.4 |

6) The 30–100 cps components prominent in the central aortic pressure pulse, as in the anacrotic wave and the incisura, result from the stiffness of the arterial walls and are damped out as they proceed away from the heart. The dicrotic wave so prominent in the peripheral pulse does not arise from this source but is an expression of the resonant wave phenomenon.

Transmission Line Model (Distributed System)

This is a useful concept in the arterial system, as in any hydraulic continuum. It is represented by van der Tweel (55) in figure 16. No matter how short or how long a given segment may be, there is always present some combination of inertance, compliance, and resistance which may be lumped in a close approximation of the behavior of that particular segment.

The performance of the transmission line is greatly affected by the relation of the terminating impedance to the characteristic impedance (52) of the line. If the terminal impedance is equal to the characteristic impedance all the energy will be absorbed and no reflections occur. The characteristic impedance, however, is frequency dependent, increasing with frequency. If the terminal Z is greater than the line Z , positive reflections will occur. Negative reflections will occur if the terminal Z is less than the characteristic Z .

Distribution of the Blood in the Aortic Arch

This is shown in figure 17. In a manner analogous to Kirchhoff's current law, the flow into the arch at any given instant from the ascending aorta is equal to the sum of the flows into the brachiocephalic and left subclavian arteries, and the flow into the descending thoracic aorta plus the uptake rate of the

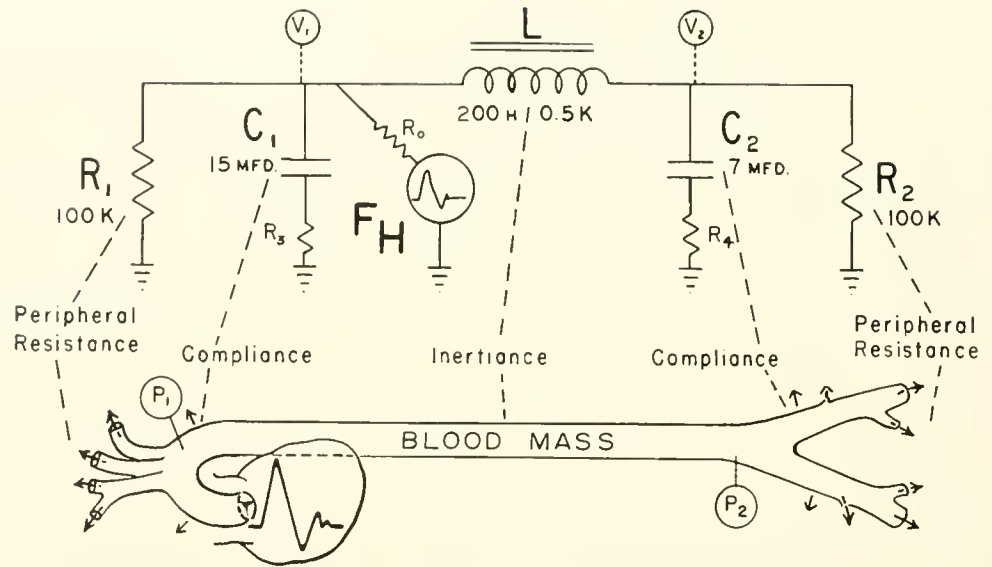


FIG. 13. The resonant network model of the arterial system. Component values indicated are those found in one typical experiment on an anesthetized open-chest dog.

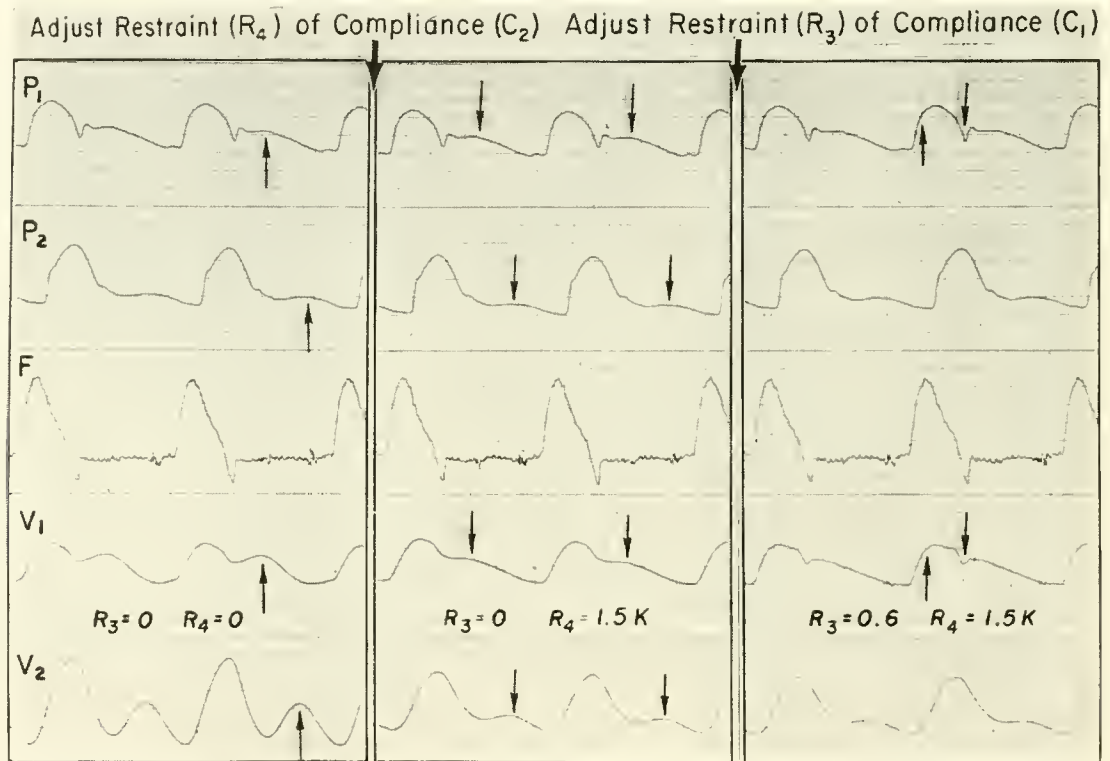


FIG. 14. Experimental testing of the resonant network model of the arterial system. P_1 = pressure in the aortic arch, P_2 = pressure in the femoral artery, F = flow in the ascending aorta, V_1 = the voltage across the capacitor C_1 to ground, V_2 = the voltage across the capacitor C_2 to ground. In the first panel the values of C_1 and C_2 have been adjusted to give the correct resonant frequency as represented in the arterial pulses. Between the first and second panels, R_4 was adjusted to give the proper damping ratio of the series resonant elements C_1 , C_2 , and L . The third panel shows the closest equivalent achieved by adjusting R_3 to reduplicate in V_1 the high components of P_1 . Delay in transmission time is not present because the simplicity of the analogue limited the number of L-C-R transmission line segments.

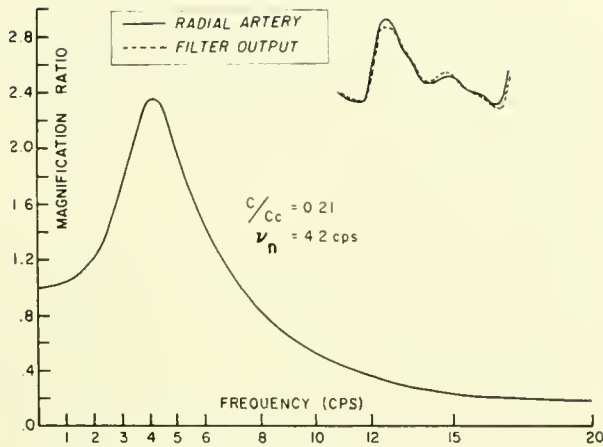


FIG. 15. Transfer function of the arteries computed by Warner (56). ν_n is equal to a resonant frequency.

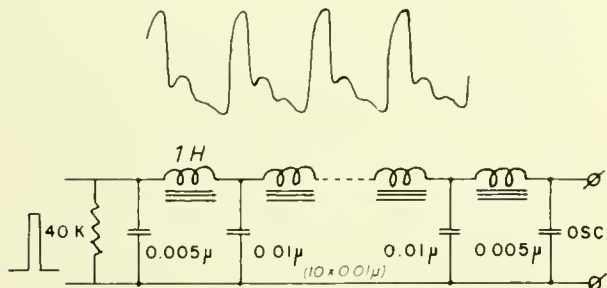


FIG. 16. Transmission line model of the arterial system, showing the stacking of L-C transmission line segments. [From van der Tweel (55).]

compliance of the arch (C_{AA}), or

$$F_{AA} = F_{Brach.} + F_{Subcl.} + F_{DTA} + C_{AA} \frac{dP}{dt} \quad (15)$$

figure 17 demonstrates this fact experimentally by comparing a plot of the instantaneous sums of $F_{Brach.}$, $F_{DTA.}$, $F_{Subcl.}$, and $C_{AA} (dP/dt)$ to F_{AA} . The value of C_{AA} was adjusted arbitrarily.

Abdominal Aorta and Its Terminal Branches

By the time the pressure and flow pulses reach the abdominal aorta, the highest frequency components are so attenuated that the flow pulses are dominated by a strong resonant wave superimposed on the mean forward flow (fig. 18). The resonant flow wave in the abdominal aorta is in phase with that in the descending thoracic and the resonant pressure wave [standing wave of Hamilton & Dow (21)] of the abdominal aorta is 180 degrees out of phase with

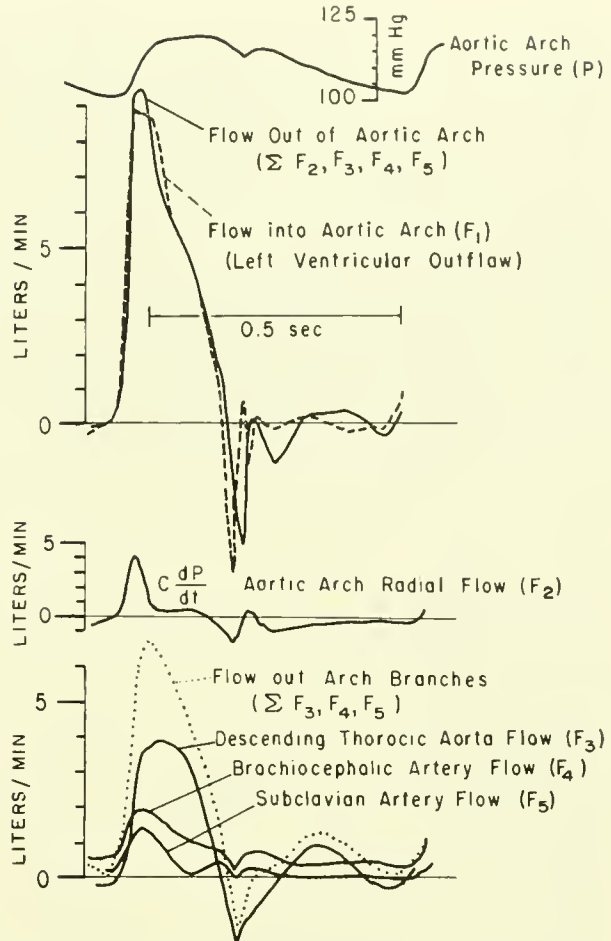


FIG. 17. Distribution of blood flow in the aortic arch in a manner analogous to Kirchhoff's current law. It is shown that the volumetric flow of blood into the arch of the aorta is equal to the sum of the instantaneous flows into the subclavian artery, brachiocephalic artery, descending thoracic aorta, and the radial flow uptake in the aortic arch. The dotted line in the lower section illustrates the branch outflows (not including radial flow).

that in the upper aorta (48). These phase relationships are similar to those of the series resonant circuit of figure 13. When the resonant flow wave reaches a maximum moving down the aorta, the attending pressure wave in the arch is falling most rapidly. When the resonant flow wave reverses, and flows at maximal rate headward in the aorta, the pressure falls rapidly in the lower aorta while it rises rapidly in the arch. There is a nodal area in the descending thoracic aorta where the pressure wave is minimal (2) and the flow wave is maximal. These findings support the resonant-network model of the arterial system.

Figure 18 demonstrates the remarkable simul-

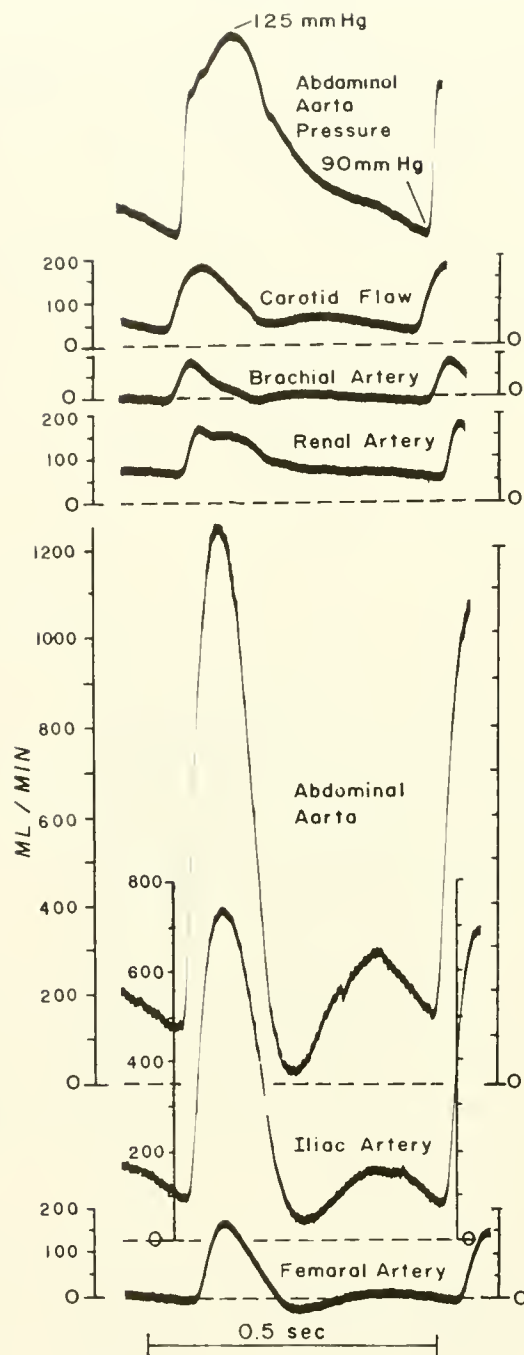


FIG. 18. Blood flow in the aortic branches. All flow ordinates are scaled equally. The contours of the various flow pulses here may be considered characteristic of the flow in the indicated branches. Carotid flow and renal flow characteristically pulsate around a mean value representing considerable continuous forward velocity. Blood flow in the femoral artery, iliac artery, abdominal artery, and brachial artery may, in the resting condition, oscillate through zero in early diastole but are also, under the conditions of muscular exercise, or metabolic demands, or vasodilator drugs, raised to a level corresponding to considerable mean forward velocity.

taneity of the peaks and troughs of the abdominal and descending thoracic aorta, iliac, and femoral flow pulses. The time of the initial rise is delayed according to the transmission time between the two points under comparison.

Function of the Resonant Wave

The finding of a large backflow component to the flow wave in the descending aorta and vessels of the extremities is at first surprising when viewed from the point of efficiency needs of the circulation. This finding, however, observed in the resting state of dogs (31), sheep (F. C. Greiss, unpublished observations), and in humans (48), disappears upon exercise of the extremities as the muscle vascular beds dilate to accommodate a greater flow.

The normal terminal impedance (peripheral resistance) of the arterial transmission line is apparently greater than the characteristic impedance during the resting state. The vasodilator mechanisms of exercise bring the terminal impedance down to and below that of the line, thereby eliminating positive reflections. Negative reflections do not arise because they are damped out by the resistance of the larger channels made more effective by increased flow. The circulation is thus brought up to more efficient operating conditions when the demands are increased. All the pulse energy passing to the periphery is completely absorbed without reflections when the peripheral resistance is decreased by exercise, injection of vasodilator drugs, and in peripheral A-V fistulas. Figure 19 illustrates the action of lowered terminal impedance in increasing the more efficient transfer of energy. Reflection from the bed beyond, seen in the control blood flow of a small artery in the dog's paw, disappears under vasodilation conditions caused by an intra-arterial injection of acetylcholine. The resonant flow wave disappears and the flow is a simpler function of the arterial pressure. Okino [see (42)] has also recorded these changes.

Renal Blood Flow

The renal vascular circuit may be, as a first approximation, compared to a simple parallel RC circuit (30). The dominant hydraulic elements of the renal artery flow are resistance and compliance, and the equation relating abdominal aorta pressure (P_1), and renal artery flow (F) is:

$$F = C \frac{dP}{dt} + \frac{1}{R} P + K \quad (16)$$

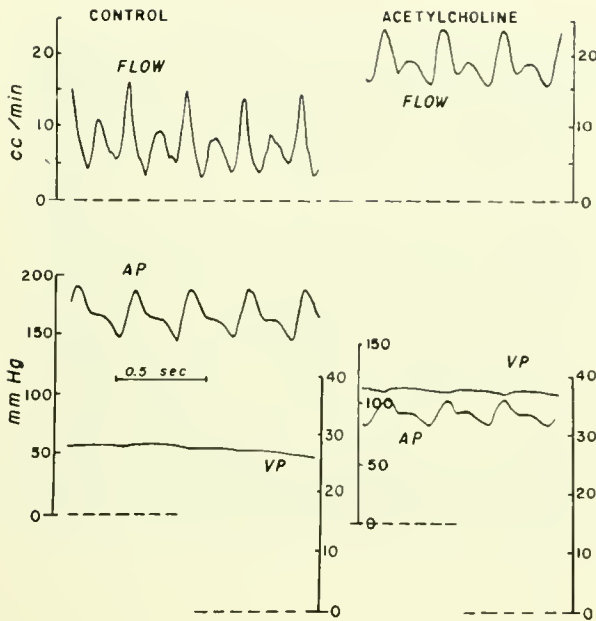


FIG. 19. Blood flow in a small peripheral artery and the effect of vasodilation. According to the definitions of the text, the control flow may be considered a resonant flow form which is converted to resistant flow form by the injection of acetylcholine into the arterial channel. *AP* represents the arterial pressure, immediately proximal to the flowmeter probe applied to a small artery in the dog's paw. *VP* represents the venous pressure in a small vein of the dog's paw. Conversion of the flow from resonant flow to resistant flow by the action of acetylcholine lowers the arterial pressure and raises the venous pressure. (Tracings, courtesy of M. C. Conrad and H. D. Green.)

$1/R$ represents the conductance at the existing pressure, and K represents the fact that the pressure-resistive-flow relationship (excluding the dynamic compliant flow term, $C(dP/dt)$), is not constant and is a nonlinear function of pressure. Presumably this results from the fact that $1/R$ is directly dependent on the pressure in a manner similar to that shown by the vascular beds of the skin. If this is true, then the relationship is:

$$F = C \frac{dP}{dt} + \frac{1}{R_{(V)} + R_{(P)}} P \quad (17)$$

where $R_{(V)}$ equals resistance controlled by vaso-motor tone, and $R_{(P)}$ equals resistance controlled by intraluminal pressure P . At present, the coefficients C , $R_{(V)}$ and $R_{(P)}$ are obtained only by measuring the flow and pressure without any means of indirect evaluation. Figure 20 illustrates one example of how C and R of equation 16 were adjusted until the dynamic flow pulse was computed from P (30). In this case flow was already known from simultaneous

measurement with the square-wave electromagnetic flowmeter.

There are apparently no positive reflections from the normal renal bed, hence the flow computed for the total renal circuit according to equation 16 and without an inertance term represents the flow in the renal artery. To compute, however, the instantaneous flow in other arteries from whose bed there are reflections one must use the difference in pressure along the artery (i.e., two pressure sources in the artery itself) and the equations 9 and 12. The most important term is then the inertial one of equation 9 although, as explained earlier, a further step in precise computation brings in the compliance of equation 12.

Carotid Artery Flow

This is illustrated in figure 18. Like the renal flow there is a large constant flow component upon which there is superimposed a dynamic component. It is related to the carotid pressure by equation 16 with the conductance term $1/R$ being the largest by far.

Because the carotid and renal flow patterns are governed largely by the resistance, they are called viscous or resistance flow patterns. The resting flow patterns of the entire aorta, iliac, femorals, and subclavian arteries are called reactance flow patterns because inertance and compliance are dominant. They have a small constant flow when compared to their dynamic component and this frequently demonstrates a period of negative flow in early diastole.

Coronary Blood Flow

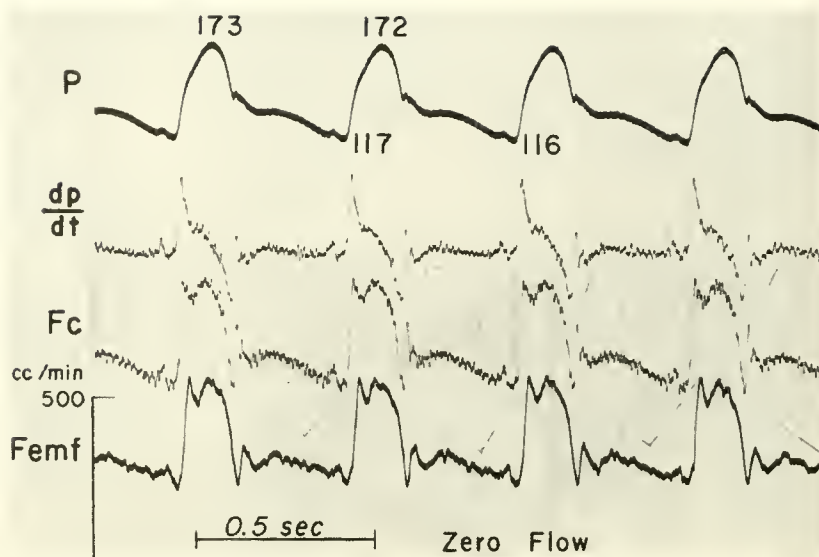
Coronary blood flow in the unopened artery was first measured by Marston and Spencer with the square-wave electromagnetic flowmeter (24). The resting patterns differ little from those of Gregg (18) who used a cannulating system and orifice meter. The equation relating coronary flow to the vascular pressures is a modification of equation 16:

$$F = C \frac{dP}{dt} + \frac{1}{R} \Delta P \quad (18)$$

where ΔP equals the aortic pressure minus the ventricular pressure minus the right atrial pressure. Figures 21 and 22 (27) illustrate the measured left anterior descending coronary flow and the circumflex coronary artery flow.

These coronary inflow curves display a marked dependence on both aortic pressure and intra-

FIG. 20. Computed renal blood flow. P = the abdominal aorta pressure at the level of the renal artery. dP/dt = the first derivative of the abdominal arterial pressure. F_c = computed blood flow using equation 16. The lower tracing is measured blood flow using the square-wave electromagnetic flow-meter on the renal artery.



ventricular pressure where coronary resistance is a complex function of vasomotor tone, intra-arterial pressure, and intramuscular pressure. The function of intramuscular pressure which reduces inflow during systole increases venous outflow during systole and may also increase capillary flow at the same time.

IV. FLOW IN THE SYSTEMIC VEINS

Phasic variations in venous blood flow result from three principle sources: 1) the beat of the heart; 2) the respiratory fluctuations; and 3) the contraction of skeletal muscle. Severe changes in position and acceleration of the body also may have profound effects on venous flow. Pulsatile flow originating from the heart beat may occur in the small peripheral veins, as a result of transmitted oscillations from the arterial system. These pulsations are generally small in the normal condition because of the damping action of the resistance of the small arteries and arterioles and the elasticity of the capillary bed. They may be accentuated, however, by vasodilatation, either by reactive hyperemia or by means of drugs, such as acetylcholine. Flow in the renal vein, normally phasic presumably because of the low renal vascular resistance, causes less damping than in most vascular beds. Great variations in blood flow within the thoracic vena cava have been recorded by Brecher (5) and others.

Effect of the Heart's Action on Vena Caval Flow

It has been shown by Gauer and Sicker [quoted in (5)] that there is an almost immeasurable gradient

in the mean blood pressure along the venae cava toward the heart. Since there is a net movement of blood in that direction, some small gradient must be present which may be sufficient, in view of the large size of the channels, to move considerable blood. It is also true, according to the principles of vascular hydraulics discussed in sections II and III, this chapter, that considerable blood may be moved by an oscillatory pressure gradient without consideration of a mean frictional gradient (fig. 23).

Atrial contraction injects a late diastolic quota of blood through the tricuspid valve and also causes a pressure transient to pass along the vena cava away from the heart. This pressure transient produces a sharp reduction in flow which may or may not cause a reversal depending upon its amplitude and the level of mean flow (fig. 24). This impediment or reversal is, however, overcome immediately by a large forward flow caused by ventricular contraction. This "vis a fronte" which draws blood toward the heart during ventricular systole arises from movement of the base of the heart (tricuspid valve closed) toward its apex, producing a transient pressure gradient in favor of flow toward the heart. Flow may be expected to follow this differential pressure transient, approximately 90 degrees out of phase.

As the base of the heart moves away from the apex during diastole, the tricuspid ring dilates and filling of the heart takes place as much by the ventricle sliding over the atrial blood as by the atrial blood flowing into the ventricle. From direct observations of the heart and from slow motion movies, it can be seen that the ventricle fills by a) dilation of the tri-

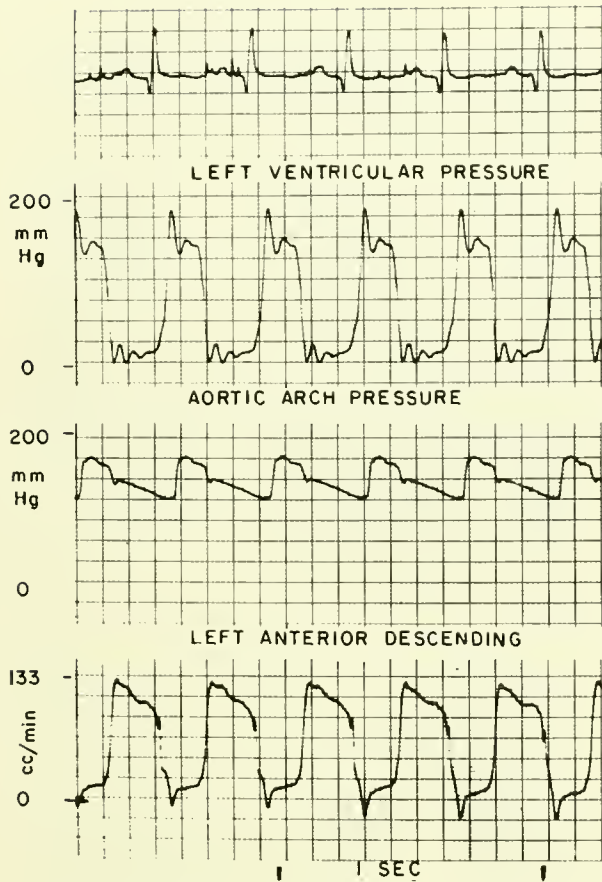


FIG. 21. Coronary blood flow in the left anterior descending branch. The upper tracing represents the electrocardiogram taken simultaneously with the left ventricular pressure, aortic arch pressure, and coronary flow. [From Schenk (43).]

cuspid ring, *b*) engulfing of the atrial blood by the right ventricle, and *c*) a final quota of blood delivered by atrial contraction. The question of whether or not the ventricle produces a sucking force during diastole is unresolved. The answer will await definitive differential pressure measurements made across the ventricular wall.

Effect of Normal Respiration on Vena Caval Flow

This is illustrated in figure 25 (28). Inspiration greatly increases the venous return as shown in the thoracic vena cava and abdominal vena cava caudal to the renal veins.

V. PULMONARY FLOW

Right Ventricular Ejection Pulse

The form of the right ventricular ejection pulse (fig. 26) differs from that of the left ventricle in

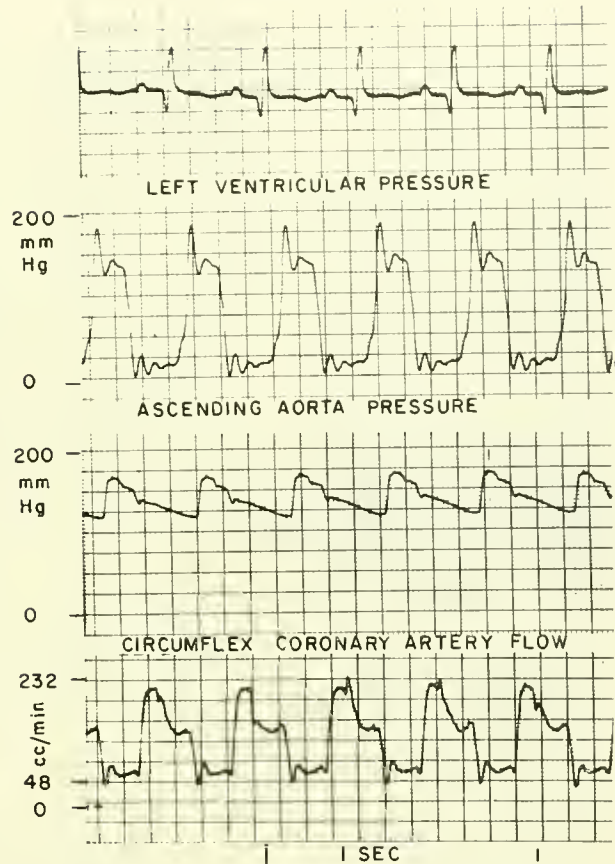


FIG. 22. Coronary blood flow in the circumflex branch. Tracings taken from the same animal as in fig. 21. [From Schenk (43).]

general by an over-all lack of the higher frequency components. The initial acceleration is slower, peak more rounded, at a somewhat lower velocity; and the reverse flow due to pulmonary valve closure forms a more rounded notch followed by a lower frequency aftervibration. There are also fewer random frequency vibrations throughout diastole. Presumably these differences arise from a slower rate of contraction of the right ventricle versus that of the left, and a greater compliance per unit of arterial wall in the pulmonary artery than that of the aorta, the latter arising perhaps from the lower distending pressure. When flow recordings are taken off the pulmonary trunk near the bifurcation, one frequently notices a low-frequency vibration during the diastolic period which may be due to some reflections from the pulmonary periphery.

Measurements of differential pressure across the pulmonary valve between the right ventricle and pulmonary artery display less of a tendency for the

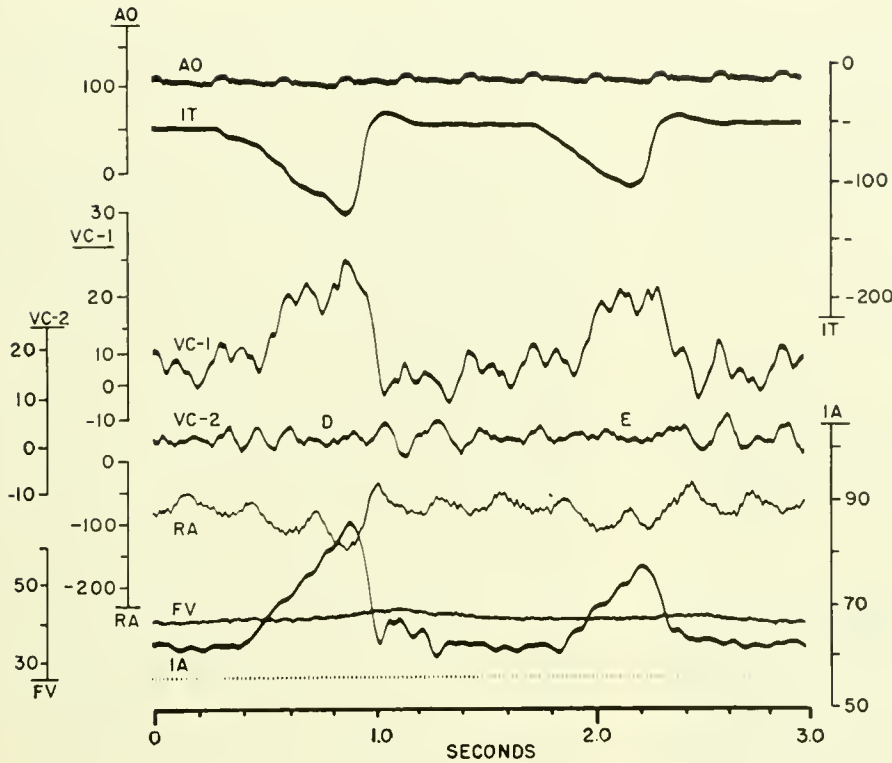


FIG. 25. The effect of natural breathing on flow in the thoracic and abdominal vena cava of the dog (closed chest). Tracings represent from above downward. *AO* = the aortic pressure in mm Hg; *IT* = intrathoracic pressure in mm H₂O; *VC-1* = thoracic inferior vena caval blood flow in ml/sec; *VC-2* = flow in IVC below renal veins in ml/sec; *RA* = right atrial pressure in mm H₂O; *FV* = femoral vein pressure in mm H₂O; and *IA* = intra-abdominal pressure in mm H₂O. [After Mixer (28).]

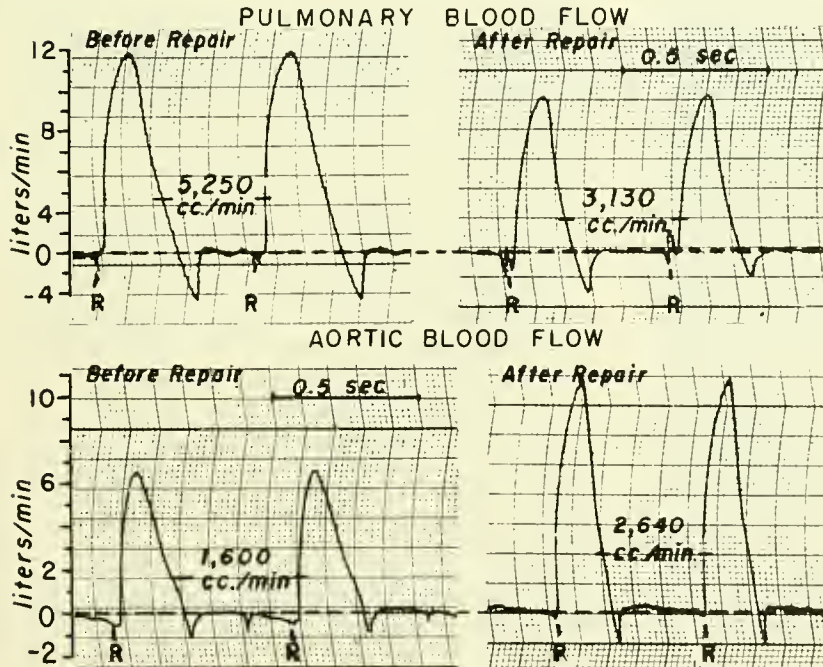


FIG. 26. Left and right ventricular ejection pulses in congenital atrial septal defect before and after repair (7-year-old boy). Repair consisted of an open-heart procedure using total cardiopulmonary bypass while closing the defect by means of a suture technique. Figures between the flow pulse tracings represent the mean output of the ventricles averaged over several heart cycles. The contour of the tracings is typical of normal tracings found in humans and dogs. Stroke volume differs markedly, however, between the two ventricles before and after repair. The repair diminished pulmonary flow and increased the aortic flow. Presumably the difference between the pulmonary and aortic flow after repair results from either 1) incomplete closure, or 2) actual difference in the cardiac output between the measurements which were not taken simultaneously.

to an internal diameter of 3 mm. Blood flow throughout these degrees of experimental coarctation was maintained at the normal level and the stroke flow was maintained primarily by flattening the peak flow

and broadening of the systolic area. During this time a systolic murmur began softly and increased in loudness and duration; its envelope maintained a contour similar to the contour of the peak of the flow

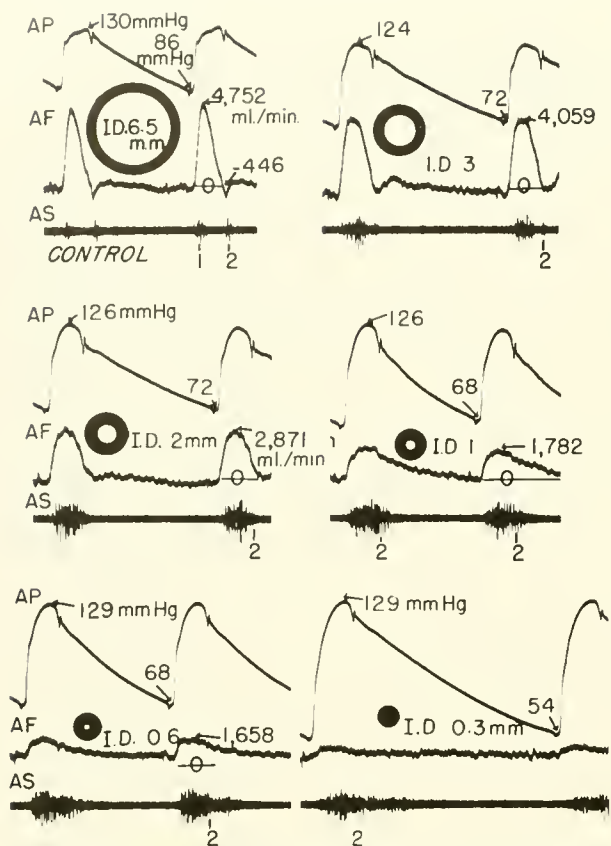


FIG. 27. Experimental graded coarctation of the descending thoracic aorta. *ID* = internal diameter; *AP* = aortic pressure; *AF* = aortic flow in the descending thoracic; and *AS* = aortic sounds. The sounds are taken by means of a barium titanate phonocatheter downstream to the point of constriction. During control, systolic pressure was 130 mm Hg, diastolic 86 mm Hg. The peak systolic flow was 4,752 ml/min, while the mean flow in the descending thoracic aorta was 446 ml/min. In spite of the reduced peak flow, there was little reduction of mean during the early stages of constriction because of change of contour of the flow pulse. The pressure gradient, flow pulse contour and murmur envelope follow the "contour rule."

pulse. Presumably, this remarkable reduction in cross-sectional area without reduction in flow is attributable to the progressively increasing gradient across the stenotic area.

Beyond this degree of obstruction any further change in the internal diameter becomes extremely critical as far as blood flow is concerned. With an internal diameter of approximately 2 to 3 mm, the murmur consistently filled systole throughout, and further reduction caused the murmur to increase in duration beyond the second sound and extend into the diastolic period. Internal diameters of 1 mm or less frequently caused a continuous, high-pitched, blow-

ing murmur distal to the site of coarctation in both experimental animals as well as in congenital lesions.

The Murmur Envelope and Contour Rule

The "envelope" of a murmur is defined as the amplitude of the full wave rectified murmur averaged over several heart cycles. The term envelope is similar to the "shape" of a murmur which itself means amplitude of the unrectified murmur. The envelope of a blowing murmur follows a "contour rule," which means that it corresponds closely to the contour of the flow pulse originating the murmur. This is true because apparently once the critical velocity is reached where turbulent flow begins (turbulence is used in a general sense to indicate nonlaminar flow), the amplitude of the resultant turbulence or lateral velocities of the nonlaminar flow is proportional to the mean axial velocity. Further, the flow under these conditions is principally viscous in nature and therefore the extant resistant pressure gradient contour parallels the flow pulse contour. The correspondence of the murmur envelope and the pressure gradient to the flow pulse exists only when the flow is highly viscous in nature (having no significant reactance flow term), and may occur without stenosis in a normal vessel under high-velocity conditions producing nonlaminar flow or in an aneurysm where nonlaminar flow may be achieved. Some examples of the contour rule are given in section VII.

General Rules Relating Murmurs to Nonlaminar Flow

From this and other studies in section VII, general rules concerning the interpretation of frequency band width and envelope (amplitude and duration) of "blowing" murmurs may be made relative to the functional anatomy of the source as follows:

1) Blowing murmurs with high pitch and low intensity are associated with small orifices through which blood is flowing at high velocity, driven by large pressure gradients.

2) Loud, blowing murmurs of relatively low-frequency spectrum, generally sounding coarse to the ear are associated with relatively large orifices through which large volumes of blood flow under relatively high-pressure gradients.

3) Very low-frequency (rumbling) murmurs of low intensity are associated with turbulent flow beyond large orifices through which blood flows under low-pressure gradients.

4) The contour of the time-intensity pattern or "envelope" of a murmur corresponds to the contour of the flow pulse passing through the region at the time of murmur production.

5) Musical murmurs, that is, murmurs with periodic reproductions in the frequency pattern as opposed to the random vibrations of blowing murmurs, arise from tissue structures, or other coherent material, set into oscillation by blood flow of high velocity.

Examples of general rule 1 are found in the continuous aortic murmur of severe degrees of coarctation and the diastolic murmur of minimum aortic regurgitation. Examples of general rule 2 are moderate degrees of coarctation, aortic and pulmonary valve stenosis, Korotkoff's sounds, patent ductus arteriosus, and the murmurs of most arteriovenous fistulae. Examples of general rule 3 are mitral stenosis, tricuspid stenosis, and occasional right atrial murmur of an interatrial septal defect. Examples of general rule 4 are really found among all murmurs wherever one compares the murmur envelope with the flow pattern as illustrated in section VII on flow in pathological conditions. Examples of general rule 5 are the vibrations of a vein wall giving rise to a "venous hum," the "sea gull" murmur arising from vibration of aortic valve cusps in aortic regurgitation, and the "moaning" systolic murmur of retroverted mitral cusps, or arising from vegetation on the mitral cusps giving rise to a systolic low-frequency periodic murmur in mitral regurgitation. In addition, musical qualities may be heard in arteriovenous fistulas which are presumably due to the vibration of the vascular wall, and are usually superimposed, like most musical murmurs, upon blowing or random noise vibrations.

VII. NORMAL AND PATHOLOGICAL FLOW PULSES IN HUMANS

The normal human flow pulses closely resemble in pattern those which have been found in the corresponding vessels of the dog and sheep. Most records of human flow pulses have been made at the time of a surgical procedure indicated because of some pathological condition. The pulses in this section presented as "normal" tracings are so called because there was no physiological reason to doubt their normalcy and second, because they correspond to those found in the experimental animal.

Flow in the Ascending Aorta

Normal blood-flow patterns are shown in figure 26. As in the dog, they show a rapid acceleration phase, a slower deceleration phase with a high-frequency (40–60 cps) backflow coincident with aortic valve closure. The volume of the flow pulse has little effect on these contour features (fig. 26) except from hypodynamic ventricles and severe degrees of exercise. Diastole is relatively uneventful with the resonant wave not appearing. The ejection pattern of the left ventricle in the presence of aortic valve stenosis is shown in figure 28. The principal deviations from normal contour seen here are a more flattened and delayed peak, with flow vibrations superimposed. In addition, there is less prominence of the valve closure backflow wave. The backflow wave incident

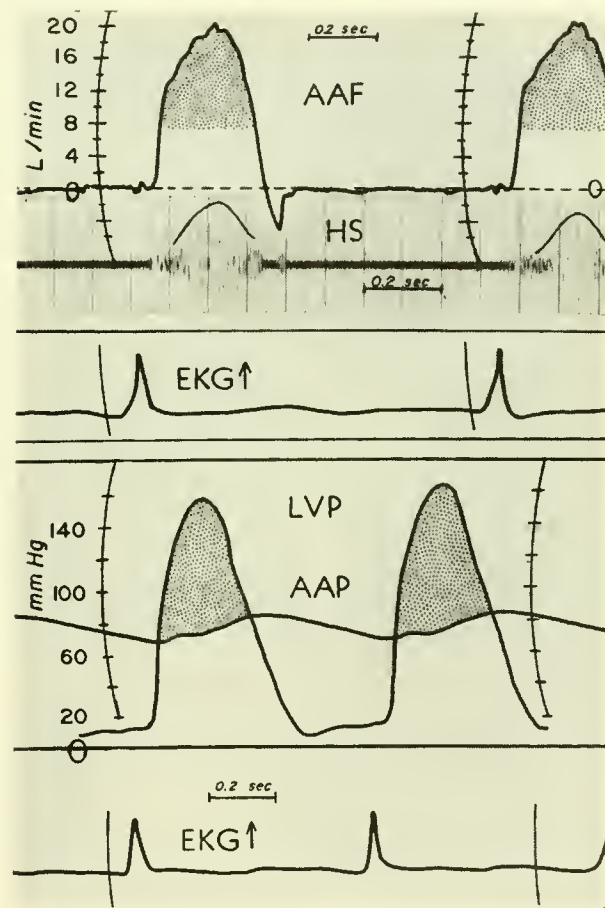


FIG. 28. Aortic valve stenosis of rheumatic origin without regurgitation in a 14-year-old boy. Measurements were made during thoracotomy prior to repair. Flow pulse shows the rounded irregular top of turbulent blood flow, corresponding to a diamond-shaped murmur and a pressure gradient between the left ventricle and ascending aorta which follows the contour rule

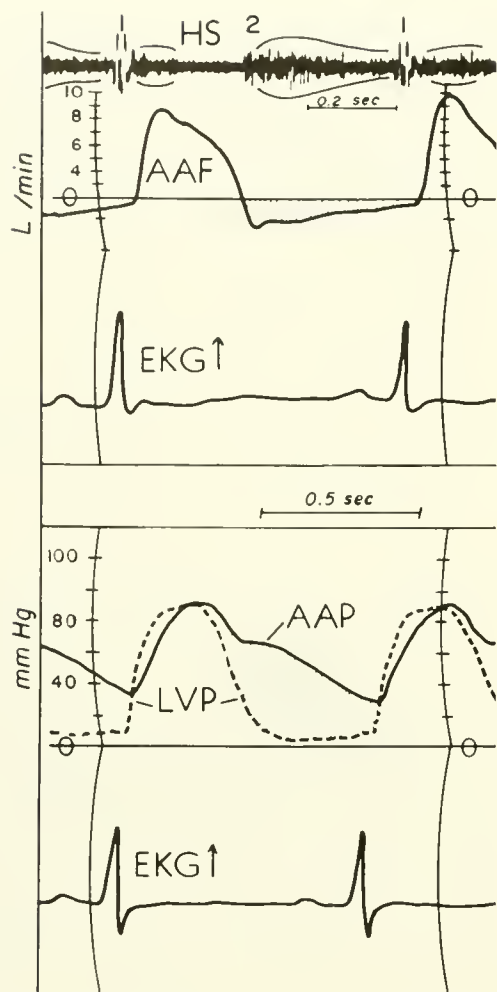


FIG. 29. Blood flow and pressure gradient in aortic valve regurgitation without stenosis in a 19-year-old girl. In ascending aorta flow, the zero reference is estimated. The regurgitant blood flow, the envelope of the diastolic murmur, and the pressure gradient between ascending aorta and left ventricle follow the contour rule. The blood flow pattern during systole is not greatly altered from that of the normal, in spite of increased stroke volume (see also atrial septal defect, fig. 26).

to valve closure is not, per se, dependent upon absence of aortic stenosis, but rather upon the degree of flexibility of the valve. If the valve is stiff and immobile, this wave will disappear. If the valve, as in congenital stenosis, is flexible, this wave will persist and also one may differentiate subaortic stenosis or outflow stenosis from valvular stenosis by the presence of a stenosis pattern during systole which retains the normal amplitude of the valve closure wave.

The severe pressure gradient across the stenotic valve, as shown by the difference in the aortic pressure and ventricular pressure when recorded directly, is

quite similar in contour to the flow-pulse contour (fig. 28). The murmur, which is harsh, loud and blowing, and is located in the ascending aorta and arch, has an envelope with a contour closely paralleling that of both the peak of the flow curve and differential pressure curve. Experimental aortic stenosis produced by means of a wire tightened about the ascending aorta at the sinus of Valsalva is shown in figure 5. The effect of varying degrees of stenosis is demonstrated on the flow curve, the aortic arch pressure, and the differential pressure between ventricle and ascending aorta. Also of note here is the heart's ability to maintain a stroke volume in the face of this severe increase in load impedance. Under the conditions of this experiment, in which several heartbeats were allowed for cardiac compensatory mechanisms to act, the left ventricle functions as a constant flow source. Further compensatory mechanisms brought into play over long periods of time, particularly allowing hypertrophy of the left ventricular wall, further enhance the heart's ability to maintain a constant stroke with a severe increase in load impedance.

Aortic regurgitation causes changes both in the systolic and diastolic contour of the left ventricular ejection pulse (fig. 29). The systolic stroke volume exceeds the normal volume by the amount necessary to compensate for regurgitation during diastole. As a result the flow pulse tends to be somewhat more rounded, but otherwise maintains the general shape of the normal pulse. However, because of the greater stroke volume, there is necessarily a greater acceleration and deceleration at the onset and termination of ejection. The valve closure notch disappears, and in its place one sees a sustained backflow deflection. The backflow, diminishing throughout diastole, is a function of the diastolic pressure gradient across the valve, and the size of the regurgitant orifice. The murmur, which has a wide frequency band extending above 100 cps, sounds high pitched and blowing, begins with reversal of the pressure gradient across the valve, usually builds up early in diastole to a maximum, and then follows a decrescendo proportional to the backflow. As seen from figure 29, the envelope of the diastolic murmur is similar to the pattern of the diastolic backflow.

Descending Thoracic Aorta

Figure 30 illustrates flow in the descending thoracic aorta immediately distal to a ductus arteriosus, before and after the closure of the ductus. The descending

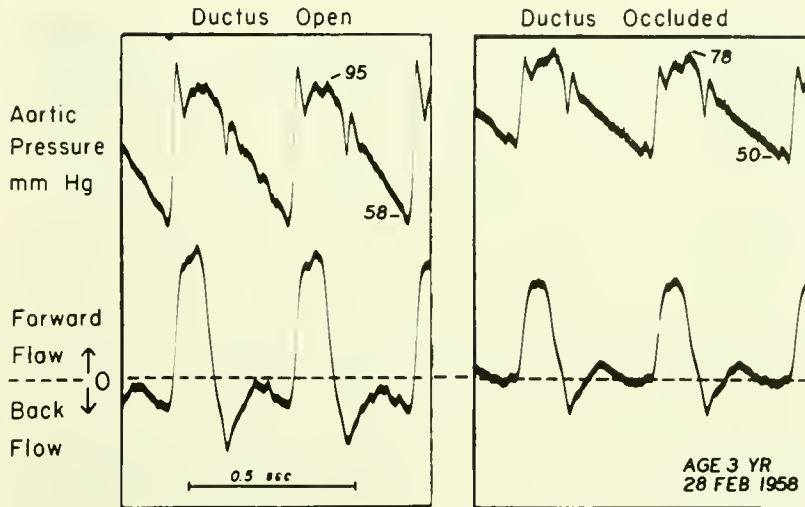


FIG. 30. Flow in the descending thoracic aorta distal to a ductus arteriosus while patent and after the ductus was occluded. Simultaneous recording of the descending aorta pressure was made by means of a needle inserted near the square-wave electromagnetic probe.

thoracic flow following closure of this ductus may be taken as the shape of the normal flow in the human descending thoracic aorta. Variations in contour show basic similarities to those of the dog's descending thoracic aorta of section III. It is of interest to note that the mean forward flow in the descending thoracic aorta distal to a patent ductus arteriosus is not affected by closure of the ductus. This finding indicates what is confirmed by flow in the descending thoracic aorta proximal to the patent ductus, namely, that the left ventricle compensates for a ductus arteriosus by increasing its output just a sufficient amount to make up for the flow passing through this

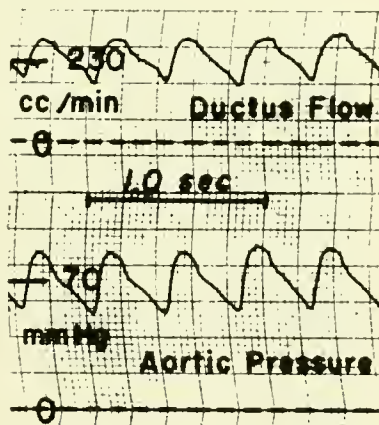


FIG. 31. Blood flow through a patent ductus arteriosus. Contour of the flow pulse follows closely that of the contour of the aortic pressure thereby indicating strong predominance of resistant blood flow in this situation. The murmur was continuous and had an envelope the contour of which followed the contour rule. Pulmonary pressures were normal.

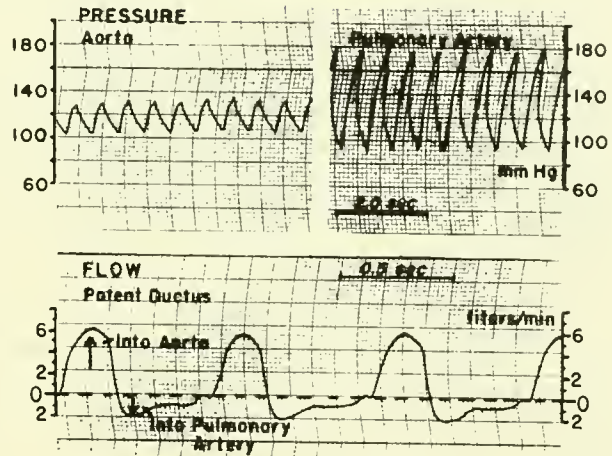


FIG. 32. Blood flow through a patent ductus arteriosus in a patient with pulmonary hypertension. There was a net flow of blood into the aorta. Flow from pulmonary artery into the aorta took place during systole, and from aorta into the pulmonary artery during diastole. The greater pulse pressure in the pulmonary artery as compared to that in the aorta undoubtedly resulted from the lower compliance of the pulmonary tree as compared to that of the systemic arterial tree. The three records: aortic pressure, pulmonary artery pressure, and patent ductus flow, were taken at different times in rapid succession.

shunt to the pulmonary artery. The flow through the ductus is predominantly viscous in type, as its contour follows closely that of the contour of the differential pressure between the aorta and pulmonary artery (fig. 31). The envelope of the murmur follows the contour rule of the differential pressure and flow pulse in a viscous flow situation. The murmur envelope and flow contour are closely represented

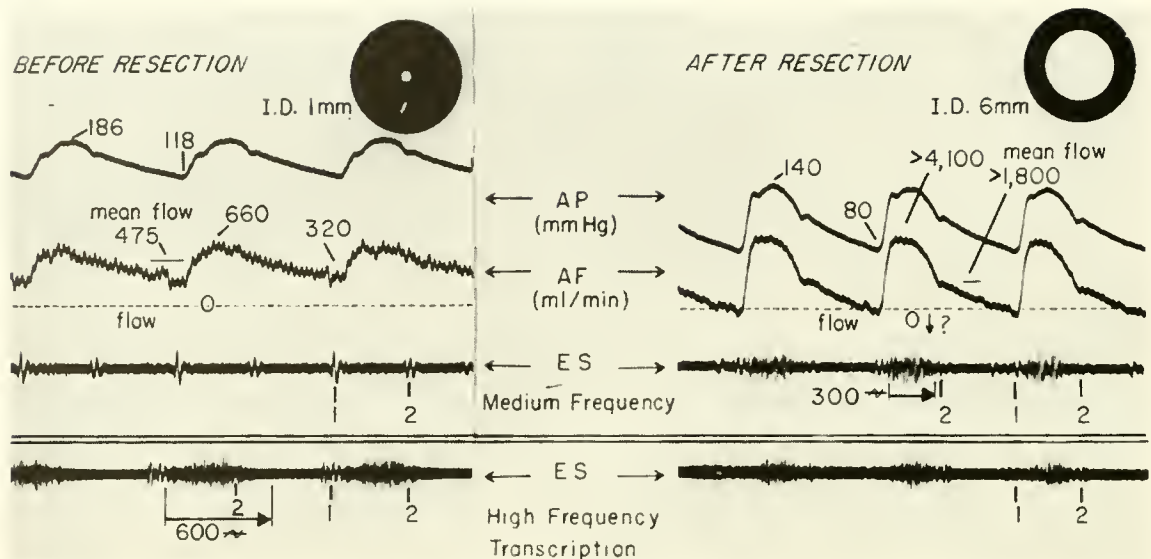


FIG. 33. Congenital coarctation. Tracings from above downward both before and after resection are: descending thoracic aorta pressure, blood flow through the coarctation area, low-frequency phonocardiogram, and high-frequency phonocardiogram. Blood flow records both before and after resection were made at the same sensitivity setting of the electromagnetic flowmeter. Zero reference after resection was not obtainable because of danger of rupture of the suture line. On the basis that zero was somewhat lower than the lowest flow point, the mean flow was estimated to be greater than 1800 ml/min after resection, while the mean flow before resection was 475 ml/min. Some constriction remained after resection and suture.

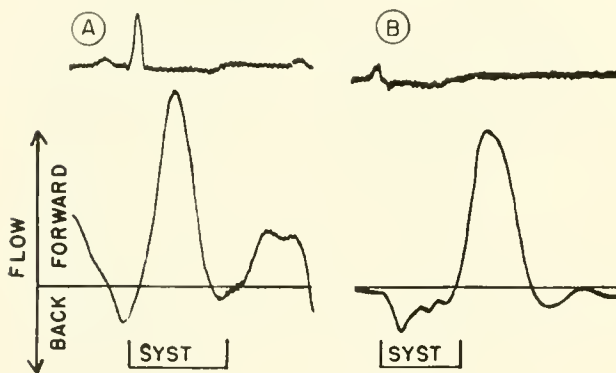


FIG. 34. Tricuspid regurgitation after the differential pressure method of Müller & Shillingford (29). Blood flow is recorded between the superior vena cava and the right atrium in a normal subject in record A, and in a patient with tricuspid incompetence and high venous pressure in record B.

by the contour of the aortic pressure pulse alone, because normally it greatly exceeds the pulmonary artery pressure at all times throughout the cardiac cycle. Because of this situation, the murmur is continuous throughout the cardiac cycle.

Figure 32 illustrates a flow pulse through a ductus of an unusual type. In this situation, chronic pulmonary hypertension had developed until the pulmo-

nary pressure exceeded that in the aorta during systole, and was less than that in the aorta during diastole. (The larger pulse pressure in the pulmonary tree than in the systemic arteries probably resulted from the smaller compliance of the pulmonary tree.) As a result, ductus flow was from pulmonary artery to aorta during systole, and from aorta to pulmonary artery during diastole.

Coarctation of the aorta also produces a viscous type flow through the stenotic region (43, 49). Most patients with coarctation have a severe degree of the type illustrated in figure 33. The differential pressure and murmur envelope both follow the contour rule with reference to the flow pulse. Flow pulses in the aortic branches are considerably altered (43).

Tricuspid Valve


Blood flow between the superior vena cava and the right atrium was measured by a pitometer by Müller & Shillingford (29). This record probably represents a close approximation of the flow pulse at the tricuspid valve except for the period of atrial contraction which is inverted to show forward flow (fig. 34).

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The anatomy and physiology of the vascular wall

HERMANN BADER  *Physiologisches Institut, Universität Würzburg, Würzburg, Germany*

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BLOOD VESSELS serve as a conducting system for the blood. They carry the blood, forced by the heart, throughout the whole body and back again to the heart. To make this possible there must be a pressure gradient with its highest values in the aorta and its lowest values in the large veins. The circulation therefore withstands a much higher pressure on the arterial side than on the venous side, a difference which is reflected in the architecture of the wall.

The stress on the vessel wall is, according to Frank (30), proportional to the blood pressure and the ratio of radius to wall thickness

$$\sigma = \frac{p \cdot r}{t} \quad (1)$$

[\(\sigma\) = stress (force per unit area), \(p\) = pressure, \(r\) = radius, \(t\) = wall thickness].

The relationship \(r/t\) and the composition of the vessel wall (fig. 1) show the level of blood pressure. For example, the aorta has a much smaller ratio of

\(r/t\) than the vena cava, which means that the difference between the wall tensions of the two vessels is less than might be expected, considering the difference between the blood pressures to which they are subjected [Burton (20)]. The relationship \(r/t\) is smaller in vessels where the principal component is smooth muscle than in vessels where the major component is elastic tissue. For that reason, the smooth muscles, the contractile elements of the wall, need to withstand smaller stress than the elastic tissue, one of the passive elements of the wall.

The vessels must be tight, so that no blood is lost on the way through the circulatory system. The vessel wall is therefore lined with the endothelium, which serves as a semipermeable membrane for the exchange of material between blood and tissue.

The arterial side of the circulatory system is not only a simple conducting system, but is also an elastic buffering chamber. The vessels, mainly the aorta, are stretched during systole, and store energy which enables them to force the blood along by elastic recoil during diastole. This ability is given the vessels by their elastic tissue. However, as Frank (31) has shown, tubing which consists only of distensible material like rubber will “blow out” at a critical pressure. This does not occur in normal blood vessels, since they have a relatively inextensible jacket in addition to the elastic tissue. This jacket is composed of collagen tissue, and is located in all arteries and veins. The collagen tissue bears the stress when the pressure becomes high, protecting the vessel from rupture or blow out.

Another quality of blood vessels is their ability to regulate the blood supply to different organs, depending on the need. When an organ is active, more blood must be carried to it than when it is at

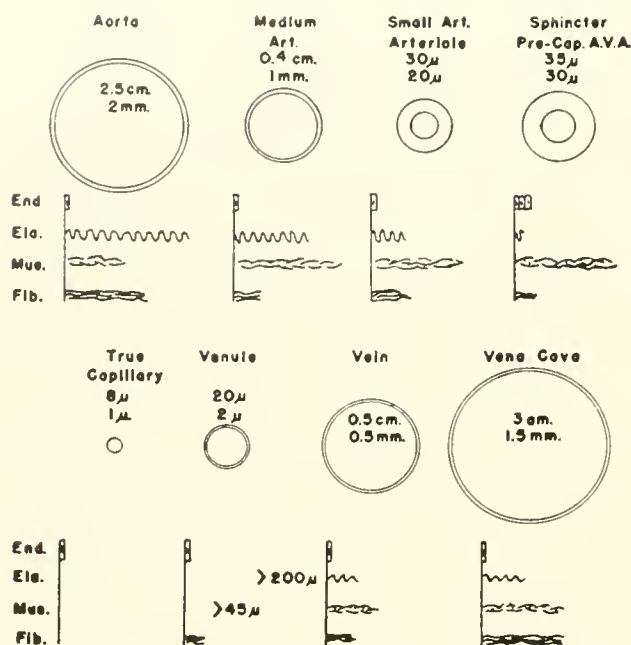


FIG. 1. Variety of admixture of the four tissues in the wall of different blood vessels. The figures under the name of the vessel are the diameter of the lumen and below it the thickness of the wall. [Burton (20).]

rest. This is best done, according to the law of Poiseuille, by changing the radius of the small supplying vessel by relaxation of the smooth muscles in the arterial wall.

Any living organ must be nourished. All but the smallest blood vessels have their own circulatory system, the vasa vasorum, which supplies blood to the vessels from the outside. In addition, simple diffusion from the inside transports nutrients and oxygen to the inner avascular layer of the blood vessel. This outward fluid shift may be aided by the radial pressure gradient through the vessel wall.

The purpose of this chapter is to discuss and to interpret these qualities and functions of the vascular wall and to explain the performance of the various wall elements in the different types of vessels.

ELEMENTS OF THE VASCULAR WALL

The terms used in this article are, for the most part, those defined by Landowne & Stacy (50). Here we will consider some of these terms in detail. Collagen tissue, elastic tissue, and smooth muscle have three qualities in common, which appear differently. These qualities are elasticity, visco-elasticity, and plasticity.

Elasticity is that property of a material which

determines its tendency, when stressed, to return to its unstressed geometrical configuration without loss of energy. If a material is completely elastic, all energy applied to it by an external straining force can be recovered as mechanical energy. Figure 2a shows an extension release cycle of such a perfectly elastic material, illustrated by a spring. Any given length has its particular tension. The extension curve and release curve are the same. It can be linear, as in figure 2a, or convex or concave to the abscissa, depending on the material stretched. Tension-length diagrams of organic materials usually show a curve which is convex to the abscissa. A perfectly elastic

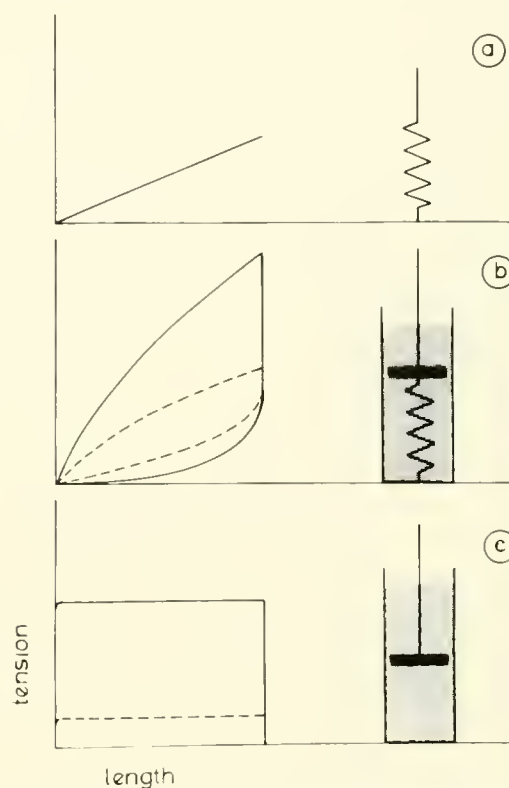


FIG. 2. Behavior with stretch of different materials. Tension and length are taken as arbitrary. *a*: Elastic material, demonstrated by a spring. Extension and release curve are the same. *b*: Visco-elastic material demonstrated by a spring, which has a brake disc on the top and which moves in a liquid. Extension and release curves inscribe a hysteresis loop, the size of which depends on the velocity of the extension and release. *Outer curve*: fast stretch; *inner curve*: slow stretch. An infinitely slow stretch gives the same curve as *a*. *c*: Viscous or plastic material demonstrated with a brake disc, which moves in a liquid. The material keeps every length to which it was brought by an external force. The force depends on the velocity of the extension. *Upper curve*: fast stretch; *lower curve*: slow stretch. In each the rate of viscous deformation is constant.

material can maintain a constant tension at any given length for an indefinite time.

Thus, the term visco-elasticity applies to materials having the combined properties of elasticity and viscosity, the elastic action being damped by a viscous one. Such a system is most easily illustrated by a spring which has a brake disc at the top and moves in a viscous fluid. The tension of such a system depends not only on the length but also on the velocity with which it is extended. The tension will be higher the faster it is stretched, and also lower, the faster the stretch is released. When the extension-release cycle of such a system is plotted with tension on the ordinate and length on the abscissa, the graph forms what is called a "hysteresis loop." Two such cycles are shown in figure 2*b*. The large loop results from a quick stretch cycle, with immediate release, the small loop from a slow stretch cycle. The area between the extension curve and the abscissa is always larger than the area below the release curve. This behavior indicates loss of energy increasing with the velocity of the stretch. More energy is required to stretch such a visco-elastic material than can be recovered during release. The area within the hysteresis loop can be expressed as percentage of the area under the extension curve. It depends only on the velocity with which the system is stretched. Rapid cyclic stretches are called "dynamic stretches," and the shape of the extension-release curves depends on the frequency of the cycles. The hysteresis loop of a pure visco-elastic element will be larger in area, the more frequent the cycles. The hysteresis should vanish if the stretch is made slowly enough, and this is called "static stretch." If the stretched material is purely visco-elastic, it returns, after an extension-release cycle, to its original length. But if it is kept at a constant stretched length, the tension will decrease with time in a hyperbolic manner until it reaches an equilibrium. This process is similar to that shown in the two curves in figure 5.

A material is called plastic when it shows the tendency to retain its new shape after deformation. Plasticity is usually understood as the quality of a material which allows it to withstand stresses of less than a critical or yield magnitude without suffering a permanent set, but which will then allow a viscous deformation with stress above this yield value. The appearance of plastic yield is not time-dependent.

Viscous or plastic behavior is illustrated in figure 2*c* by a disk which is moved in a viscous fluid. The force required depends upon the velocity with which the disc is moved. The top curve in figure 2*c* is derived by a quick movement of the disc, the bottom curve by

a slow movement. As long as the velocity remains constant, the stress will be constant too. If the applied force is removed, the stress decreases without reducing the length. In contrast to the behavior of a visco-elastic element, a viscous or plastic element will never go back to its original shape by itself.

The systems shown in figure 2*a*, *b*, and *c* are very much simplified models to describe the physical definitions of elastic, visco-elastic, and plastic properties. These properties reflect, in organic materials, their complicated molecular structure. In organic materials there is usually a combination of the three qualities described, with elastic, visco-elastic, and plastic properties behaving as though arranged in series, and present in different amount. Such a combination is described by the term "elastic incompleteness."

For instance, if an elastic and a visco-elastic element are in series, then the element which offers the smaller resistance to extension will dominate the stretch behavior. Since the resistance of the visco-elastic element is greater at high rates of stretch, the properties of this series combination is determined more by the elastic element. The more frequent are the stretch cycles, the less is the hysteresis. If there is also a purely viscous or a plastic element in series, after every stretch cycle the material assumes a greater length. There is also the possibility that many visco-elastic and viscous elements may be in series, each having a different rate- and time-dependency. Such combinations of elastic, visco-elastic, and plastic elements can show a very slight rate-dependency, if, for instance, the elastic element offers the smallest resistance to stretch when compared with the other elements present. Because of the visco-elastic or plastic units, the system may show a great time-dependency, which occurs as an elastic aftereffect or a relaxation when the material is kept on a constant stress or length.

The viscosity of organic materials may not only derive from a viscous flow within the tissue, but also from an architectural rearrangement involving the uncoiling or slippage of twisted elements. Such processes may be involved in the phenomenon of the "stable loop" seen in elastic arteries after a number of stretches, which does not show any rate or time-dependency but does depend on the existing tension level [Remington (73); see also Chapter 24]. The so-called viscosity or plasticity of organic materials may be complicated, and thus not follow the physical definitions. Further, there is usually a certain polarity to these tissues in that tension-length relations are different in various directions. Most organic materials

cannot be extended ad infinitum, but tear at a certain length.

Smooth muscle is a special case. It can be elongated like a purely plastic material and can behave at any given length like an elastic or visco-elastic material. But it can also recover its original length by contraction. This means that the plastic property of smooth muscle can be neutralized or hindered, leaving only the elastic or visco-elastic elements under stress, as a result of the action of the contractile element. [For further details see Reichel (71).]

Endothelium

The circulatory system is lined almost completely by a single layer of very thin polygonal-shaped cells, the endothelium. This forms a tight, smooth surface on the inside of the vascular wall and serves as a semipermeable membrane for the interchange of materials between blood and tissues. It has a high distensibility. Its ability for regeneration is very good. For instance, 3 weeks after implantation aortic grafts show a smooth continuous lining of endothelial cells, which presumably are built from fibrocytes [Petry & Heberer (67)]. A detailed discussion of the qualities of the endothelium is given in Chapter 29.

Collagen Tissue

Collagen tissue is produced by fibroblasts, which are located in all connective tissues. The probable precursors of collagen fibers are the reticular fibers. These are argyrophilic fibers which are found especially in places where collagen fibers are forming, as around aortic grafts. They both show a banded appearance under the electron microscope [see Wassermann (95)]. The collagen fibers consist of a network of long protein chains which are linked by H bonds and ionic bonds. This network is filled with an amorphous substance (mucopolysaccharide). Smaller fibers are glued together to larger fibers by a cement substance which is continuous with the ground substance.

This structure gives the collagen fibers a very high elastic modulus and also makes them very flexible [see Harkness (36)]. Collagen fibers are nearly 25 times as strong as elastic tissue but 15 times less extensible (table 1). Collagen fibers are found in all vessels, spread over the whole wall. They appear in the unstretched vessel wall as wavy bundles, but some of them become straightened if the pressure within the vessel is raised above the mean blood pressure [Reuterwall (74)]. This anatomical design, together with the

TABLE 1. *Elastic, Visco-Elastic and Plastic Behavior of Collagen and Elastic Tissue (102)*

| | Maximal Tensile Strength, kg/cm ² | Maximal Extension, in % | Irreversible Elongation in % of Total Elongation | Hysteresis in % of Area Under Stretch Curve |
|------------------------------------|----------------------------------------------|-------------------------|--------------------------------------------------|---------------------------------------------|
| Collagen tissue (tendon) | 660 (250-750) | 10 (5-12) | 67 | 57 |
| Elastic tissue (ligamentum nuchae) | 25 (12-45) | 150 (120-220) | 19 | 60 |

high elastic modulus, enables them to form a "jacket" [Burton (20)], which is put in action only when the fibers are straightened, by increased intraluminal pressure. Thus the collagen fibers are not strained by the normal blood pressure; they serve as a safety factor for the vessels and keep them from "blowing out" at high pressure.

Only the collagen fibers increase in number with aging, replacing frayed elastic fibers and degenerated smooth muscle cells [Meyer (58), Kobayashi (46)]. Since the elastic and muscular tissues originally supported the wall tension at normal blood pressures, the replacing collagen fibers must take over this task [Bader & Kapal (7)] with the result that the wall becomes less distensible. This is compensated until the sixth decade of life by enlargement of the diameters of the vessels involved [Simon & Meyer (86)]. However, collagen tissue, when overloaded, does show elastic incompleteness, which means that it is to some extent a plastic material (table 1). The fibers do not return to their original length immediately after extension and the residual elongation can be 67 per cent of the total elongation. This plasticity may produce a large hysteresis. It may be that such plastic property can account for the increase in vessel volume seen in aging.

Ground Substance

The ground substance has the properties of a colloid—it is water-insoluble, but can bind water. It consists of the mucopolysaccharides: hyaluronic acid and chondroitin sulfate. It is likely that chondroitin sulfate forms the cement substance which binds collagen fibers together, and hyaluronic acid serves as a lubricating material [see Harkness (36)]. Such a lubricating substance is necessary in the vessel wall, since the fibrous elements of the wall (collagen fibers,

elastic fibers, and smooth muscles) must be able to slide past each other with minimal friction during the pulsatile expansion of the vessel. The ground substance is a very viscous material and it probably contributes to the typical visco-elastic behavior of distensible vessels.

Elastic Tissue

Elastic tissue is a rubberlike material with high extensibility. It contains the protein elastin without any detectable amount of carbohydrate [Lansing (52)]. In contrast to collagen tissue, it is an extremely insoluble material, and is not influenced by boiling or autoclaving. X-ray diffraction and electron microscopy do not ordinarily show any internal organization in elastic fibers. It is therefore assumed that the protein fibrils lie without orientation within the fibers [see Lansing (52)]. This disorder gives the elastic tissue its high extensibility. It can be extended to twice its original length, but its tensile strength is 1_{20} to 1_{30} that of collagen tissue (table 1). This explains why it must be protected from excessive elongation and tearing in the vascular wall by the much stronger collagen fibers.

Elastic tissue forms fenestrated membranes which lie one over the other in elastic vessels. These membranes serve as footholds for the tension muscles (fig. 3). There is less elastic tissue in the more peripheral muscular vessels. It is only a very minor component in the arterioles and precapillary sphincters (fig. 1). Elastic fibers appear in the veins, increasing in amount as they near the heart. They are partly straight and partly wavy in unstretched vessels. The wavy ones become straight before the collagen fibers straighten out as the pressure rises [Reuterwall (74)]. At ordinary pressures the elastic tissue supports most of the tension in elastic vessels, whereas this task is performed by smooth muscles in the muscular vessels.

Elastic tissues usually fray with age. This is a normal change which appears in all vessels of old people. Calcification of the fibers is also progressive with age. In addition, the fibers undergo fragmentation, which finally leaves little more than dispersed granular material [see Lansing (52)]. Calcification is especially great in arteriosclerosis. However, Lansing (52) has shown that the percentage of elastin in the vessel wall does not decrease with age, while the calcium content rises in the human aorta from 0.4 per cent in the second decade to 7 per cent in the eighth decade. Frayed and fragmented elastic fibers remaining cannot support the wall tension at normal pressures. This



FIG. 3. Axillary artery (human). Irradiation of tension muscles in the elastica externa—*a*: in situ; *b*: elastica externa artificially lifted off. Muscle endings fasten on the elastic membrane. [Benninghoff (10).]

task is taken over in old age by collagen fibers, which are under stress with ordinary blood pressure [Bader & Kapal (7)]. Thus, the distensibility of the vessels decreases, but the volume of the aorta increases and its total elastic uptake may remain within normal limits so long as the increase in volume keeps pace with the decrease in distensibility [Kapal & Bader (44), Simon & Meyer (86)].

Smooth Muscle

The smooth muscle cell is an elongated spindle with a single elongated nucleus in the thickest part of the cell. The cells vary very much in size. In the vascular wall they are between 20 and 50 μ in length, with their greatest diameter between 5 and 10 μ . There are two types of smooth muscles in the vascular wall: "Spannmuskeln" (tension muscles), which are described in detail by Benninghoff (10, 11), and ring muscles.

The tension muscles are connected to elastic fibers and membranes, using them as tendons (fig. 3). They can thus raise the tension on the elastic tissue in the vessel wall by contraction (fig. 7) and so affect the blood pressure (see Arteries of the Elastic Type,

below). The smooth muscles of the aorta and the pulmonalis are almost exclusively tension muscles. But the proportion of tension muscles diminishes toward the periphery. The smallest arteries and arterioles have almost no tension muscles. They may appear again on the venous side of the circulatory system, but not in as large numbers as in the elastic arteries [Grau (34)].

The ring muscles are connected with each other. How they are related to the elastic and collagen tissue is not certain, but it is very likely that they have slack connections with both tissues. Since smooth muscles are almost completely surrounded by reticular fibers, it is possible that these fibers bind them together. The ring muscles form the greatest part of the wall in the muscular vessels, where they form a helical arrangement [Fischer (23), Schultze-Jena (84)]. Arterioles and precapillary sphincters consist mostly of ring muscles.

Smooth muscles have the general quality of spontaneous activity and self-conduction [see Bülbiring (17)]. Bozler (16) has concluded from this behavior that they form a syncytium, which would mean that the individual muscle cells are interconnected by protoplasmic bridges. But in reality they form a network in which every muscle fibril is surrounded by its own membrane, so that there are double membranes at places where the cells are in contact with each other [see Prosser (68)]. This network acts like a functional "syncytium," since an excitation can be conducted over the double membranes. This double membrane has a high resistance, and therefore the conduction in smooth muscles is much slower than that in nerve fibers. The conduction can be propagated over the whole organ, as in the uterus or the ureter (single-unit smooth muscles), or it can be limited to a certain area, as in the intestine [Bozler (16), Greven (35), Bülbiring (17)]. The limitation results from the presence of a higher resistance of the double membranes at certain places. The resistance can be changed so that the area which responds to a stimulus can be increased or decreased. Another characteristic of the syncytium is its response to stretch [Bülbiring (17)]. If smooth muscles of the intestine are stretched, the membrane depolarizes and spikes are produced (fig. 4). Contraction occurs and tension rises in direct proportion to the increase in spike frequency. But in addition to having independent conductivity and excitability, smooth muscles also receive innervation from both the sympathetic and parasympathetic nerve system. There are ganglion cells around the adventitia [Leontowitsch (55)] and nerve fibers in the media [Boeke (15)] of the

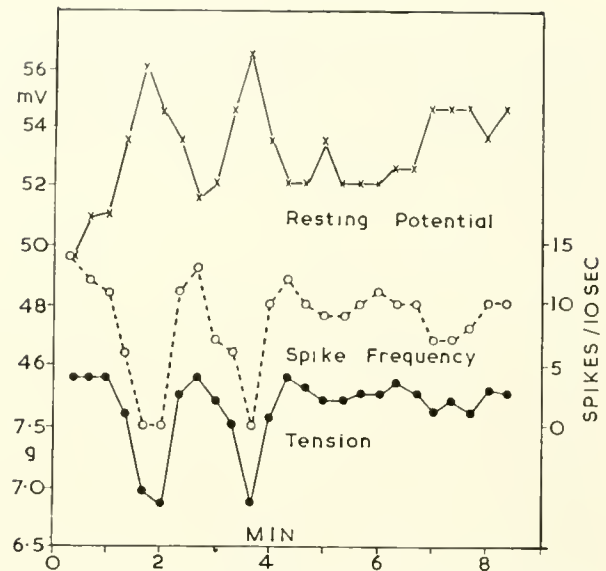


FIG. 4. Graph showing correlation between membrane potentials, spike frequency, and tension during spontaneous pendular rhythm recorded for 10 min. [Bülbiring (17).]

blood vessels [see also Staubesand (87)]. The autonomic nervous system can change the spontaneous activity of the smooth muscles by changing their membrane potentials.

In addition to the syncytium-like smooth muscles, there are also multiple-unit smooth muscles which are neither self-conducting nor spontaneously active. They receive extensive innervation and appear to be organized in some type of motor-unit plan [see Prosser (68)].

Little work has been done on the problem of the excitation and conduction of vascular smooth muscle. Therefore it is hard to say whether it represents a multiple-unit system or a syncytium. Monnier (62) has shown that the conduction of excitation in the mesenteric artery of cattle (an artery of the muscular type) is very slow (only about 2 mm/sec). This is much slower than the conduction of any known nerve, and in a range similar to other syncytium-like smooth muscles [see Bülbiring (17)]. The mesenteric artery also responds to stretch with a contraction. It may be assumed therefore that the muscles in the peripheral arteries behave as a syncytium. This is likely, in view of the relationship of blood pressure to flow. For instance, Thureau & Kramer (91) have shown that the flow in the kidney becomes constant if the pressure is raised above 90 mm Hg. This special flow-pressure relationship is due to an increase of resistance, effected by contraction of the smooth muscles in the preglomerular arteries. Similar behavior in the arteries of

the extremities is reported by Folkow (26). This idea has a long history, beginning with the contribution of Bayliss (9) in 1902.

It may be assumed that the contraction of smooth muscle is caused by the increase of tension in the vascular wall as a result of the rising blood pressure. There is no adaptation to the tension stimulus, which agrees with the results of Bülbbring (17) on the intestinal smooth muscle. Folkow (28) suggests that the tonus of the resistance vessels is maintained by myogenic activity of their smooth muscles, which are excited by the tension of the wall (similar to the case for intestinal smooth muscles shown in fig. 4). However, this autoactivity, in both types of smooth muscle, is controlled by the autonomic nervous system. Since the smooth muscles in the peripheral arteries are mostly ring muscles, it may be that the ring muscles can behave like a syncytium. The tension muscles are always interrupted by elastic fibers, and Prosser *et al.* (69) have found a much larger intercellular distance between the individual muscle cells in vessels of the elastic type than in other organs (1000 nm in the pig carotid artery as against 120 nm in the cat intestine). It is therefore very likely that they form a multiunit system in which the muscle cells receive extensive sympathetic and parasympathetic innervation. This impression is confirmed by Burnstock & Prosser (18), who got no response to stretch from the carotid artery, a vessel of the elastic type, or from the renal vein.

Over and over the idea appears in the literature that arteries may contract and relax as quickly as the heart and so force the blood to the periphery just as the intestine propels a bolus to the colon. One of its newer proponents, Dickinson (22), shows a contraction curve of a sheep's hepatic artery which develops its peak tension in about 3 sec after an unphysiological stimulus of 120 v. The slowness of contraction and the long latency speak against the possibility of the propulsion of blood by arterial contraction. This latter attitude is shared by Fleisch (25) and Wetterer & Kapal (99).

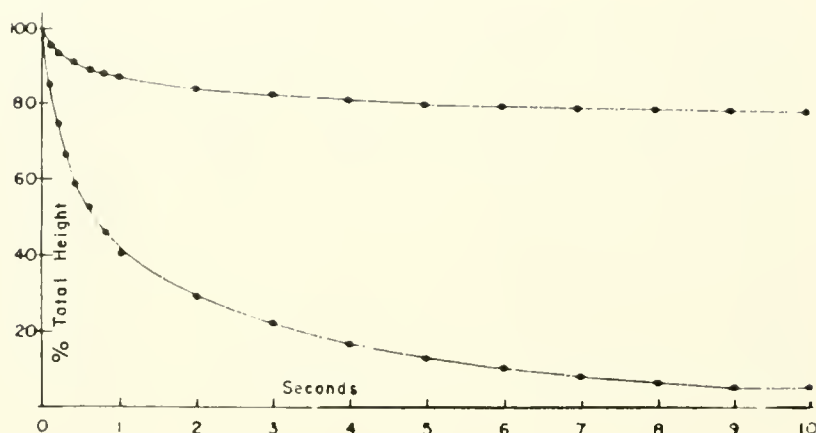
If smooth muscles are extended slowly they behave like a plastic material. They can maintain a given length, either short or long, for protracted periods with very low metabolism. However, this length maintenance does depend upon repeated stimulations of constant magnitude. If the stimulation is increased, these muscles respond by contracting, regardless of their initial length (except, of course, if already maximally contracted). From this it follows that there must be some mechanism which enables smooth muscle to shift its behavior from plastic when "set" in length to

visco-elastic, when contracting. Üxküll (93) has postulated for this a "Sperrung" (catch mechanism), signifying that the protein filaments within the muscle fibers "catch" at a certain length so that they cannot slip apart when tension is applied.

Three possible explanations have been offered for this behavior. The first, suggested by Reichel, is that the smooth muscle consists of two elements in series, an elastic element and a contractile element, where the contractile element can behave with either plasticity or contractility (70). If this is true, the "catch mechanism" could be described as a transformation of plasticity to contractility, where the element is "caught" at any length and thus is able to keep a given tension with a low metabolism or to contract. An alternative to this theory, suggested by Lowy & Hanson (56a), is called the sliding filament mechanism. They assume that thin discontinuous actin-containing filaments move relative to thick discontinuous paramyosin-containing filaments, as in striated muscles. Linkages are presumably formed during contraction between both filaments all of one type, with one rate of formation. The rate of breaking can vary from slow (tonic contraction, visco-elastic) to fast (phasic contraction, plastic) depending on the concentration of a relaxant present (i.e., 5-hydroxytryptamine). Repeated excitatory stimulation could maintain these linkages, whereas stimulation of inhibitory nerves could increase the rate at which they break [Lowy & Millman (57)]. A second possibility is that the plastic and the contractile elements are in parallel, with an elastic element in series. In such an arrangement the catch mechanism could be in the plastic element, whereas the contractile element could cancel any plastic deformation by contraction. Such a parallel arrangement is postulated by Johnson (41a). He assumes that the contractile system is formed by the actomyosin, and that paramyosin is situated parallel to it as the plastic element. Laszt (54) assumes a similar mechanism in the vascular smooth muscle. A third possibility is that the plastic and contractile elements are in series. In such an arrangement the contractile element could work only if the catch mechanism were put in action. But it would then be necessary to have a special mechanism to cancel the plastic deformation, such as the presence of both fast and slow contractile elements within the smooth muscle, the slow elements being virtually "plastic."

Whether any of these three mechanisms may be the real one is not clear. It is possible, too, that one smooth muscle may work by one mechanism and

FIG. 5 Average stress-relaxation curves of carotid and umbilical arteries. Vertical coordinate is given in percentage of total pressure rise, following injection. *Upper curve*, common carotid artery of the dog. *Lower curve*, umbilical artery of the human. [Zatzman *et al.* (103).]



others by another, since, for example, the uterus and the bladder are very different in properties and action [Bader (3)].

If a smooth muscle is stretched quickly to a certain length, it will show a tension increase. If this length is held for a longer time, the tension will decrease, at first quickly, later more slowly. This typical stress relaxation is a result of the visco-elasticity of the smooth muscle, which may be due to breaking of the linkages within the myofilaments. A typical stress-relaxation curve of smooth muscles is like that of the lower curve of figure 5. For further details of the mechanical properties of muscles, see Reichel (71).

If these mechanical properties of smooth muscles are to be compared with those of the vascular wall, one must keep in mind the modifying effects of collagen and elastic tissue [Remington (73)]. Another point is that most of the experiments with smooth muscles are made on organs other than blood vessels, *in vitro*, and without innervation. Smooth muscles *in vivo* are under a continuous stimulation, and they are also under constant contraction and tension in the vascular wall. It is therefore very likely that the smooth muscles of the vessel wall *in vivo* would show different visco-elastic and plastic behavior from those found during *in vitro* experiments.

Zatzman *et al.* (103) have shown that there is a great difference in the stress-relaxation behavior of the elastic carotid artery and the muscular umbilical artery. After 10 sec of stress, relaxation of the carotid artery amounts to about 20 per cent of the original tension, whereas in the umbilical artery it is about 95 per cent (fig. 5). This indicates that in the umbilical artery the tension is applied mostly to smooth muscle with its large visco-elasticity and plasticity. It is not easy to say to what degree smooth muscle is respon-

sible for the relaxation of the carotid artery, since elastic and collagen tissues may each have both a visco-elastic component (hysteresis loop during stretch cycle) and a plastic component [irreversible elongation (table 1)]. This passive behavior is responsible in part for the stress relaxation of elastic arteries [see Kapal (42)].

Smooth muscle tissue degenerates and decreases in amount with age, and is replaced by collagen fibers [Meyer (58), Kobayashi (46)]. This tends to render the arterial tree more rigid and to explain the systolic hypertension of old age. The high systolic pressure in this condition puts an extra burden on the heart. [See Bader & Kapal (5) and the paragraphs on elastic arteries below.]

Smooth muscles have the ability to regenerate. For example, Petry & Heberer (67) have described cell formations which are found on the inside of aortic grafts some weeks after implantation. These cells seem to be muscle cells, and are assumed to originate from fibroblasts.

DIFFERENT TYPES OF VESSELS

Vessels differ in their architectural structure and their behavior according to their varied tasks. There are, in general, four different vessel types: on the arterial side are elastic arteries and muscular arteries, but it is hard to say where the one ends and the other begins, since the structural changes are gradual. Usually the aorta, the pulmonary artery, the common carotid artery, the subclavian artery, and the common iliac artery are regarded as elastic arteries. Arteries more peripheral than the above, down to the arterioles, are classed as muscular arteries. After these are the capillaries, which consist mostly of endothe-

lium. Then there are veins, which are built to some extent like the arteries. The most striking difference between them is their mounting, for most arteries have a slack connection with the surrounding tissues, whereas the veins are more intimately bound up with the surrounding tissues to make a functional system.

Arteries of the Elastic Type

The wall of the elastic arteries is characterized by a high percentage of elastic tissue (fig. 1), which may be 40 per cent of the wall in the thoracic aorta, but decreases toward the periphery. The elastic tissue is mostly present as fenestrated membranes—up to 50 membranes located one upon the other. There are also star-shaped membranes in the wall of the pulmonary artery [Meyer (59)]. There is a network of elastic fibers between all these membranes. The membranes are connected by smooth muscles, the tension muscles, described by Benninghoff (10, 11). These tension muscles use the elastic membranes as footholds (fig. 3). There are no ring muscles in the thoracic aorta, but they appear in increasing numbers in the more peripheral arteries. Where the ring muscles exceed the tension muscles in amount the arteries are called muscular arteries. The collagen fibers are distributed over the entire wall. They lie there in wavy bundles, which become straight if the blood pressure rises over the normal mean value [Reuterwall (74)].

The large amount of elastic tissue and looseness of the collagen fibers give elastic arteries high distensibility. For instance, the aorta can be distended to a threefold increase in contained volume over that at

zero pressure. This high distensibility enables an elastic vessel to act as would an air chamber (Windkessel). The aorta contributes over 50 per cent to the total vascular air chamber action [Wetterer (98)]. If an elastic artery is stretched, it shows a typical S-shaped pressure-volume diagram, like that in figure 6 where “static” stretch curves are given for the thoracic aorta of a pig. [See Chapters 7 and 24 for the explanation of the typical S-shaped pressure-volume diagram of elastic arteries and its relation to the tension-length diagram. [See also Frank (30, 31).] A similar S-shaped curve may be obtained from a rubber tube within a nylon tube, where the nylon tube serves as a “jacket” [Bader & Kapal (6)]. In such a pressure-volume diagram the rubber tube is responsible for the curve below the inflexion point and which appears concave to the abscissa; the nylon jacket for the convex part above the inflexion point. This fact, together with the finding of Reuterwall (74) that when elastic tissue becomes straight collagen tissue is still wavy (i.e., still relatively unstretched) and the study of Roach & Burton (75) which involved differential digestion of collagen and elastic fibers of the iliac artery, indicates that the part of the pressure-volume diagram from zero pressure to the inflexion point reflects the extension of elastic tissue, whereas the part above the inflexion point is due to the collagen tissue [see Bader & Kapal (7)].

The upper curve of figure 6 is derived from a stretch curve made shortly after death, after the aorta was stimulated with epinephrine; the lower curve was made 8 days later when the smooth muscles were dead. Schöenberger & Müller (83) got similar results on cow aortas with dynamic stretches. Millahn & Jaster (61) stretched pig and cow aortas after relaxing the smooth muscles with acetylcholine, finding that the stretch curve lay below the curve given by the stimulated vessel. The pressure-volume diagram can shift to higher or lower pressures depending on the contractile state of the smooth muscle, but the shape of the curve never changes. This proves that smooth muscles can increase the wall tension without changing the elastic properties of the vessel, a finding which Benninghoff (10, 11) had proposed as a result of his microscopic studies. Bader & Kapal (5) concluded from their experiments that smooth muscle can be arranged neither in series with the elastic elements nor in parallel. Both arrangements would give, with stimulation, not only a shift of the stretch curve to higher pressures, but also a change of the shape of the curve.

Since the tension muscles are attached to the elastic

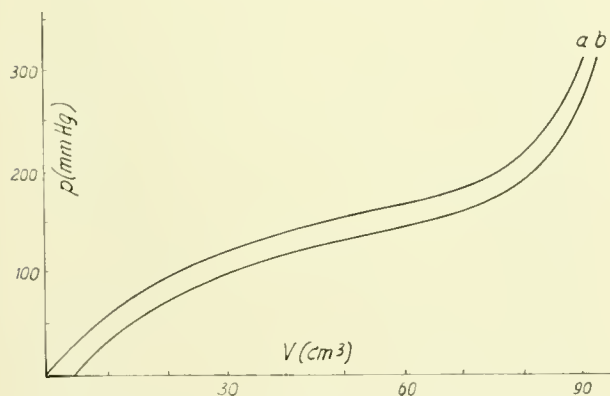


FIG. 6. Pressure-volume diagram of the thoracic aorta of the pig. *a*: Extension curve made shortly after sacrificing. The aorta was stimulated with epinephrine. *b*: Extension curve made 8 days later. Smooth muscles were dead. [Bader & Kapal (5).]

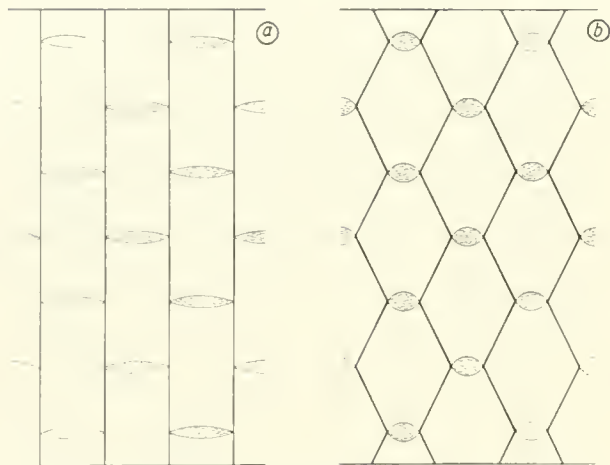


FIG. 7. Model for the arrangement of tension muscles and elastic tissue. Stretch in vertical direction. *a*: Tension muscles relaxed; *b*: tension muscles contracted. [Kapal & Bader (43).]

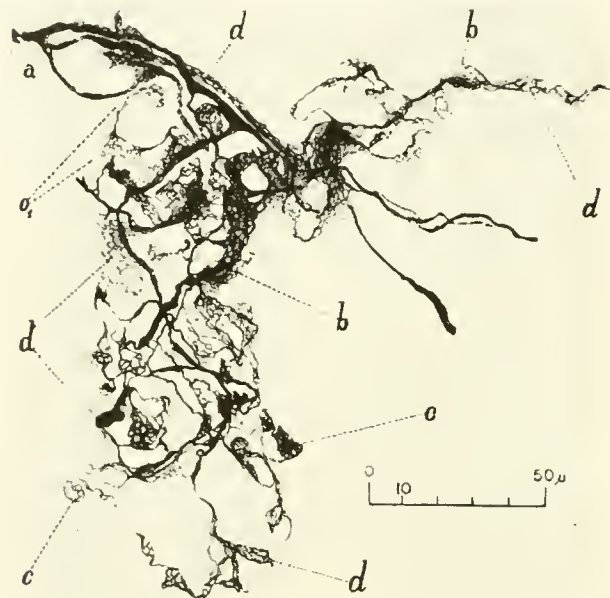


FIG. 7A. Baroreceptor in the adventitia of the human aortic arch. *a*: End fiber of the aortic depressor nerve; *b*: network; *c*: end network; *d*: neurofibrils. Method after Bielschowsky. $\times 1100$. [Ábrahám (1).]

membranes, and the contraction of the smooth muscles seems to influence only the part of the curve which is ascribed to the extension of elastic tissue, Kapal & Bader (43) have designed a model which is similar to an arrangement which Burton (20) had published in 1953 in his highly stimulating review article. It shows the action of the tension muscles in elastic arteries.

In figure 7*a* the smooth muscles are relaxed; in 7*b*, they are contracted. The smooth muscles fasten

on the elastic fibers or membranes at right angles to the direction in which the elastic fibers are stretched. These fibers become elongated by contraction of the smooth muscles, but the circumference of the vessel is not changed (fig. 7*b*). The consequence is a rise in the tension of the elastic fibers. Since the model will be involved in a stretch in the direction of the elastic fibers, the tension muscles do not need to develop tension as great as the total wall tension, but can increase the stress on the elastic tissue with relatively little work.

This model has an advantage to neurophysiologists as well as to muscle physiologists. Heymans & Delaunois (37) have shown that the blood pressure decreases if the smooth muscles of the carotid sinus are stimulated by noradrenalin. Heymans *et al.* (38) obtained the same results by elongating the carotid sinus. They concluded from these experiments that the pressoreceptors located in the carotid sinus, which cause a decrease of the mean blood pressure after stimulation, do not respond to the blood pressure, but rather to the wall tension [see Heymans & van den Heuvel-Heymans (39)]. It is very likely that the pressoreceptors situated in the aorta work in the same way.

The pressoreceptors appear as a very fine network of neurofibrils (fig. 7*A*). They are mainly located in the adventitia of the carotid sinus [Sunder-Plassmann (89)] and in the adventitia and the outer part of the media of the aortic arch [Seto (85)]. Stöhr (88) has the impression that this network of neurofibrils shown in figure 7*A* may be only a part of the whole neurofibril mass of which the pressoreceptor is constituted. He assumes that smaller fibrils exist but are not visible because of limitations in the staining method and in the optical properties of the light microscope.

There are very few clues as to how the network of the pressoreceptor is related to the surrounding tissue. Sunder-Plassmann (89) has shown that the media of the carotid sinus is thinner than that of the nearby vessel, but the membrana elastica externa is thickened. The elastica externa in the carotid sinus shows a sharp boundary separating it from the media, but a more gradual merging with the adventitia. In this diffuse zone, which shows collagen fibers and large elastic membranes, the pressoreceptors of the carotid sinus are located, and the neurofibril networks show a certain degree of adaptation to the shape of the connective tissue. Ábrahám (1) describes the neurofibril networks of the aortic arch as nestling flat against the vessel wall. Their position follows the direction of the fibrous elements.

It may very likely be that in both the carotid sinus and the aortic arch, the neurofibril networks of the pressoreceptors are in one way or another attached to the connective tissue, especially the elastic membranes or fibers. Thus the pressoreceptors are assumed to be parallel to the elastic membranes or fibers, an assumption which agrees with the facts now available. They will be stimulated if the smooth muscles increase the tension of the elastic tissue by contraction. But now the stimulated pressoreceptors reflexly lower the blood pressure until the tension of the elastic fibers, and with them that of the pressoreceptors, decreases again to the normal value (equation 1). The tension muscles are thus able to change the blood pressure, as shown in the work of Bader & Kapal (5). The model of Kapal & Bader (43), and the results of Heymans *et al.* (37-39) agree very well. It also fits very well with the idea that the tension muscles are multiple-unit muscles, since they are a type of control organ which does not depend on the wall tension.

The model may also explain the higher resistance and blood pressure of older people in contrast to younger people. Smooth muscles degenerate with age and are replaced by collagen fibers [Meyer (58), Kobayashi (46)]. This means that the smooth muscles are no longer able to stretch the elastic tissue as much as in younger individuals. But if the tension of the elastic tissue is lowered by lack of smooth muscle function, the blood pressure will rise until the tension reaches a physiological value for the pressoreceptors. As the muscles continue to degenerate, the pressure needed to stimulate the receptors continues to rise, and this may be one of the various mechanisms which cause essential hypertension. Such a hypertension must be called "essential," since the weakness of the tension muscles cannot be diagnosed and there may be no clearly diagnostic anatomical change of the arterial wall. The only evident sign of such muscle weakness would be the hypertension.

However, in the aging process degeneration of smooth muscles, fraying of elastic tissue, and increase of the collagen tissue are accompanied by a decrease in the distensibility of the arteries. A 20-year-old aorta can be distended to 300 per cent of its zero-pressure volume, but a 90-year-old aorta can be distended only about 25 per cent [Simon & Meyer (86)]. If the inflexion point of the volume pressure is high and the curve reaches its slope of maximum distensibility at about 100 mm Hg (the normal mean blood pressure) (cf the 13-year-old aorta in fig. 8a), the work required of the heart is reduced in maintaining a physiological pressure level. If the inflexion

occurs at a lower pressure level, as after an increase of collagen tissue (older aortas), the mean blood pressure falls on a steeper slope of the pressure-volume curve. Under this condition the heart would have to work more were this disadvantage not compensated by enlarging the volume of the aorta. Figure 8a shows a fivefold increase in the volume at 100 mm Hg between the 13-year-old and the 85-year-old aorta. The volume change of the elastic chamber with each heart beat, that is, the volume which can be injected to give the physiological pulse pressure amplitude, remains nearly constant until about the sixth decade of life, as a result of the initial volume increase. This means that the heart work need not increase with the decrease of the wall distensibility [Simon & Meyer (86)]. The aortas over 60 years do not show any inflexion point; they are convex to the abscissa from the very beginning. This signifies that collagen tissue is already stressed near zero pressure. The pulmonary artery shows similar behavior, but the inflexion point occurs at a lower pressure, just as the pulmonary pressure is lower [Meyer & Simon (60), Frasher & Sobin (32)].

The ratio of radius to wall thickness, which is important in the relationship of the wall stress to the blood pressure (equation 1), is the same at zero pressure in aortas of different ages [Hieronymi

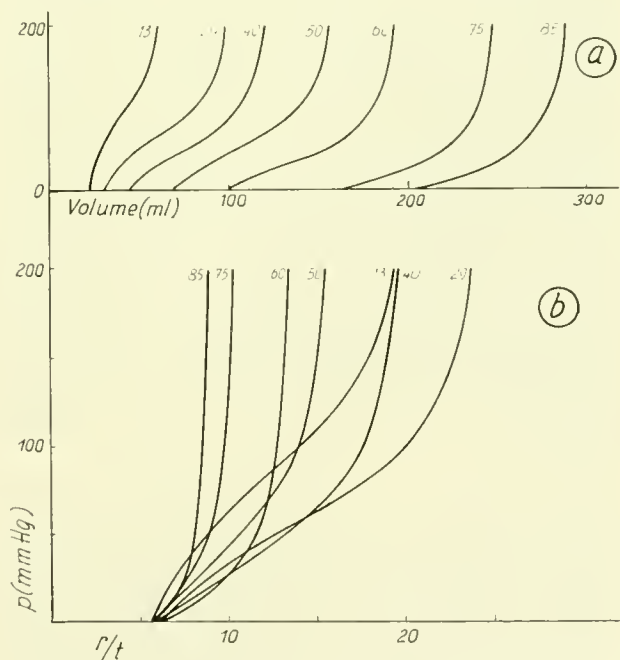
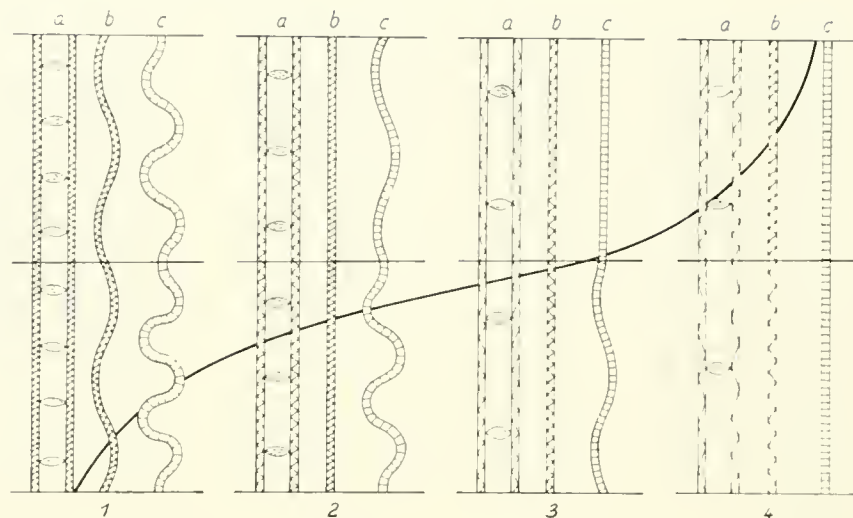


FIG. 8. *a*: Pressure-volume diagrams of the thoracic aorta of the human at different ages. *b*: The relationship of radius to wall thickness of the same aortas in relation to the pressure. [Bader (4).]

FIG. 9. Schematic presentation of the behavior of the different tissues in the wall of elastic-type vessels at different degrees of extension. Description in the text. [Bader & Kapal (7).] The stretch is in the vertical direction. The S-shaped line is the pressure-volume curve of a young human aorta.



(40)], but at 100 mm Hg this ratio is age-dependent (fig. 8*b*). It increases from the first decade of life until the end of the third decade and decreases from then until the end of life. The shift of this ratio, like the shift of the inflexion point, is caused by the increase of the collagen tissue. The arteries become more and more rigid with age. A rise of the blood pressure in older people does not change the tension on the elastica, and thus prevents stimulation of the pressoreceptors. This indicates that the regulation of the blood pressure of old people would become more and more unstable [Bader (4)]. Since the decrease of the ratio of radius to wall thickness in the aging aorta simultaneously decreases the wall tension (equation 1), the tension of the pressoreceptors must also become lower and lower. But this process may result in an increase of the mean blood pressure to get the pressoreceptor again on the normal tension level. A similar change has already been mentioned with the degeneration of the tension muscles. But since the changes in smooth muscles, and in the ratio of radius to wall thickness, with aging, are greater in proportion than the usual increase of the mean blood pressure, one may assume also a change in receptor sensitivity.

The interaction of the three wall elements in the elastic arteries, elastic tissue, collagen tissue, and smooth muscle, may be illustrated by the scheme of figure 9. Sections 1 through 4 represent different stretch phases. The stretch takes place in vertical direction. Both halves of each phase must be regarded together. The element *a* represents two elastic fibers which are connected by smooth muscles as in figure 7. Both elastic fibers are already straight at zero pres-

sure. The element *b* is an elastic fiber which is still wavy (unstressed). Both *a* and *b*, in the upper and the lower half, are under minimal stress. Element *c* is a collagen fiber. In the upper half it is less wavy than in the lower half. Phase 2 will be reached after the stress has begun. Element *a* is already stressed, whereas element *b* is just straightened. By this means the recruitment of the elastic fibers is represented. The stretch proceeds in phase 3, so that collagen fibers are partly straight and included in the stress (upper half). The collagen fiber in the lower half is still wavy. Elastic fibers only are stressed in phases 1 and 2, whereas elastic and collagen fibers are functional in series in phase 3. Now the length available for further stretching of the elastic fibers is only half as much as in phases 1 and 2, since a further stretch of the elastic fibers in the upper half is prevented by the collagen fibers. This means that the increase in extension, per unit rise in pressure, becomes less and the pressure volume diagram, which until now was concave to the abscissa, becomes convex. At last a point is reached where all collagen fibers are straight: phase 4. Elastic and collagen fibers are straight and parallel. Since collagen tissue is much less distensible than elastic tissue, the wall distensibility at this point depends only on collagen tissue. This model illustrates the wall architecture of a proximal elastic artery. The more peripheral the vessel, the more the ring muscles participate and the more the model of figure 9 will be combined with the model of figure 13 (see below).

The effect of changes with age in the arterial wall can be illustrated by having the stretch start in phase 2, 3, or 4. Thus unextensible elements are put in action at lower pressures than in young arteries

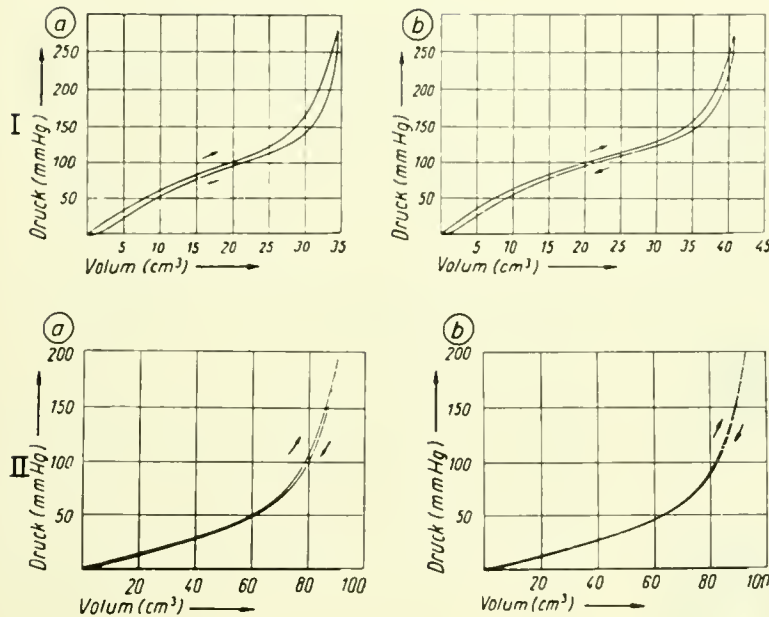


FIG. 10. Extension-release curves of the thoracic aorta of the human at different ages and with different numbers of stretches. I: 14 years old—(a) 4th stretch cycle; (b) 100th stretch cycle. II: 63 years old—(a) 3rd stretch cycle; (b) 15th stretch cycle. [Wagner & Kapal (94).]

[Bader & Kapal (7)]. The unextensible fibers might be collagen fibers or calcified elastic fibers which are under stress with small extension of the arterial wall [Roach & Burton (76)] or even with no extension at all.

Elastic vessels, like any tissue, show typical visco-elastic and plastic behavior. An extension-release cycle gives a hysteresis loop which depends in part on the velocity with which the stretch was applied [see Remington (72)]. There is also a shift, on repeated stretching, of the pressure-volume diagram toward greater volume at the initial pressure level, indicating some plasticity. Wagner & Kapal (94) have found with experiments on the human aorta that hysteresis is not only dependent on the stretch velocity, but also on the age of the vessel (fig. 10). It becomes smaller, the older the vessel is. The same effect appears if an aorta is stretched repeatedly. The more frequently the artery is stretched, the smaller is the hysteresis. The hysteresis is greater above the inflexion point of the pressure-volume curve than below [Wagner & Kapal (94)].

In large elastic vessels, contraction of smooth muscles does not influence the hysteresis [Remington (72)]. Kapal (42) has shown that the aorta responds to dynamic stresses as would collagen and elastic tissue, but not like smooth muscle. Therefore, it seems that the visco-elastic and plastic behavior of elastic arteries depends mostly on elastic tissue, collagen tissue, and ground substance, but only to a small degree on smooth muscles. This is confirmed by the

curves of figures 6 and the model in figure 7, where smooth muscles do not affect the mechanical properties of the vessel (see also fig. 5). However, in the more peripheral vessels the increasingly plentiful ring muscles have a correspondingly greater effect on visco-elastic behavior [see Peterson *et al.* (66), Bergel (12, 13)]. The greater elastic incompleteness of collagen fibers, as compared to elastic fibers (see table 1), agrees very well with the larger hysteresis in the upper, collagen-dependent part of the pressure-volume diagram. But with both collagen and elastic tissue, the elastic incompleteness seems to diminish as more stretch cycles are made. The similarity between decrease of the hysteresis with age and with repeated cycles has led to the assumption that, as a result of their elastic incompleteness, the vessels are distended more and more by the pulse pressure during their life, until they reach a stable state, eliminating the visco-elastic and plastic elements [Wagner & Kapal (94)].

Vessels of the Muscular Type

The more peripherally the arteries are located, the higher is the percentage of smooth muscles in the wall (fig. 1). In elastic arteries one cannot distinguish easily between intima, media, and adventitia, whereas in muscular arteries there is a clear separation of these layers. The media consists mostly of smooth muscles, the ring muscles. Between them are collagen and elastic fibers. The elastic membranes, typical for the

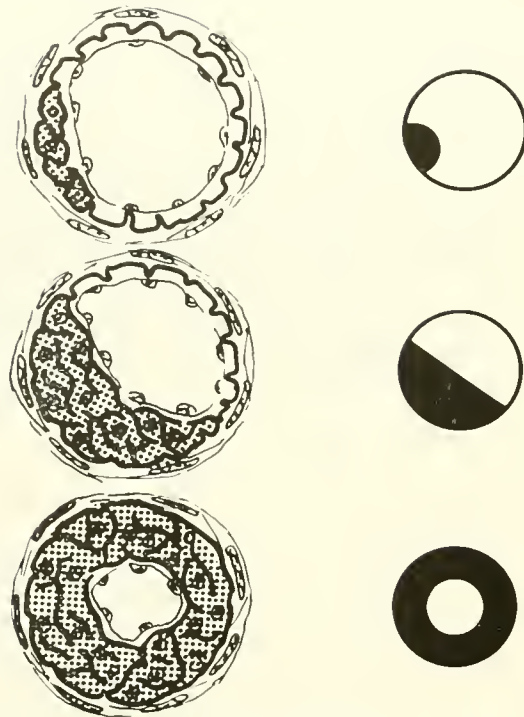


FIG. 10A: Longitudinal muscles in the intima of the branches of the bronchial artery. Schematic presentation of their different arrangements. [Weibel (97).]

elastic vessels, are concentrated in the elastica interna, which separates the intima from the media, and in the elastica externa, which separates the media from the adventitia. Attached to these membranes are the tension muscles, but they account for but a small percentage of the total vascular smooth muscles [Benninghoff (10, 11)]. The ring muscles are arranged in the wall in a helical structure [Schultze-Jena (84), Fischer (23)].

Arteries which are frequently extended in the longitudinal direction, like the branches of the bronchial artery of the lung, possess longitudinal muscles in addition to the ring muscles [Weibel (96)]. These longitudinal muscles are situated in the split membrana elastica interna and can be arranged either in fairly thick one-sided bundles, or as concentric shells which surround the whole lumen (fig. 10A).

The mechanical behavior changes in the same way as the anatomical picture, smooth muscle forming the major support of muscular arterics, elastic tissue of elastic arteries. In contrast to the elastic vessels, the muscular arteries can change their radius over a wide range. The smallest vessels, like the arterioles and the precapillary sphincters, can even close their lumens completely. Figure 11 shows pressure-dia-

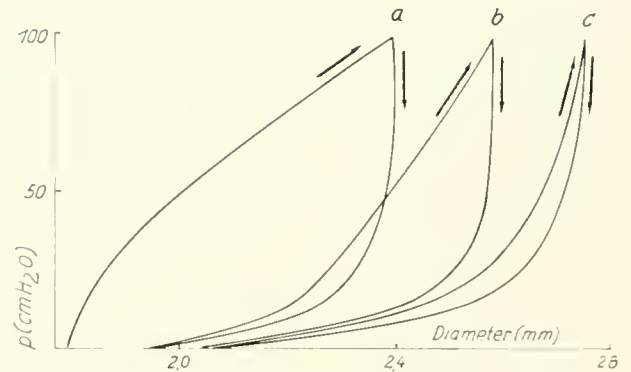


FIG. 11: Pressure-diameter diagrams of a small branch of the mesenteric artery of the horse—*a*: 1st stretch cycle; *b*: 2nd stretch cycle; *c*: 6th stretch cycle. [After Wezler & Schlüter (100).]

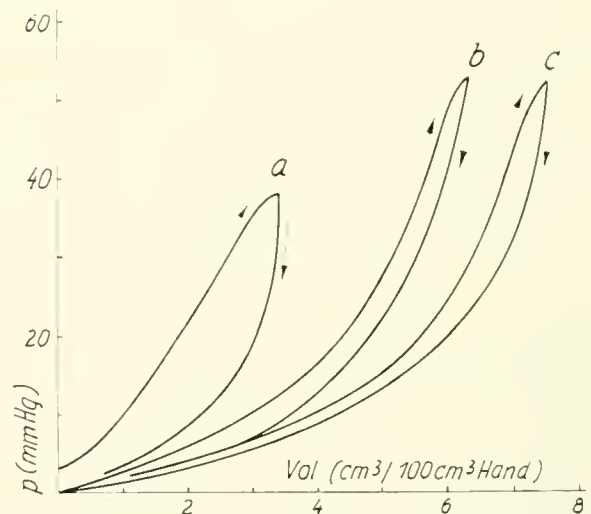


FIG. 12: Pressure-volume diagrams of the vessels of the hand: an in vivo experiment. *a*: Temperature in the plethysmograph: 25.5 C (vessels contracted); *b*: temperature 31.5 C (vessels normal); *c*: temperature 36.0 C (vessels relaxed). [After Thron *et al.* (90).]

ter diagrams of a small branch of the mesenteric artery of the horse [Wezler & Schlüter (100)]. Six extension-release curves are made successively, the first, second, and sixth being shown. During the first stretch cycle the smooth muscles are assumed to be contracted, during the following cycles they are more and more relaxed. The first extension-release curve shows a large hysteresis, where the extension curve is concave to the abscissa and the release curve is convex. This indicates a very large visco-elasticity of the vessel wall, and very different behavior from that of elastic-type vessels for which the extension and the release curves have a similar shape. Later extension-release cycles show smaller hysteresis, and the exten-

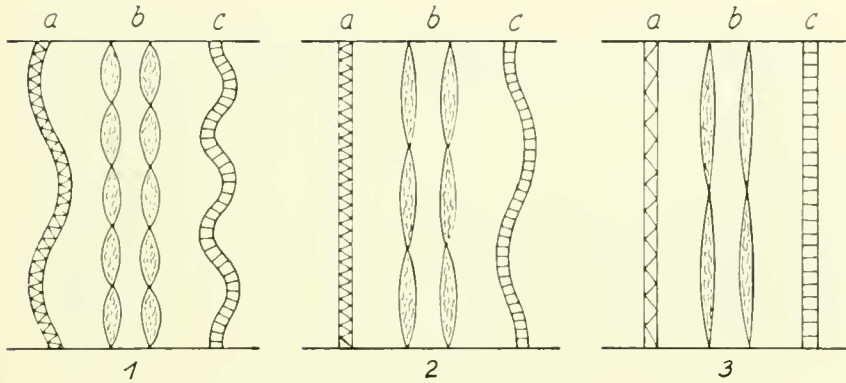


FIG. 13. Schematic presentation of the behavior of the different tissues in the wall of muscular vessels with different degrees of extension. Description in the text. [After Wezler & Schlüter (100).]

sion curves also become convex to the abscissa. Schlüter & Wezler (80) have described other curves where the first extension curve had an S-shape or was convex to the abscissa. In all these cases the shape of the diagram seems to depend very much on the state of contraction of the smooth muscles. The extension diagram will be concave to the abscissa if the smooth muscles are contracted, and the slope of the curve will be steeper the stronger the contraction. If the smooth muscles are less contracted, the extension curve will show an S-shape or be concave to the abscissa. The whole diagram moves with frequent stretches to larger diameters or volumes, but comes back to the original place if the smooth muscles are stimulated. Thron *et al.* (90) obtained similar results *in vivo*. Figure 12 shows plethysmographically obtained pressure-volume diagrams of the human hand vessels at different states of contraction of the vascular muscles, due to different temperatures. The extension curve of the constricted vessels (*a*) is nearly straight and is followed during release by a large hysteresis. The less constricted vessels have less hysteresis with both distention and release convex to the abscissa. This agrees very well with the diagrams of Wezler & Schlüter (100), which were made *in vitro* (fig. 11).

The diagrams shown in figures 11 and 12 are in many ways different from the diagrams in figures 6, 8, and 10, which were made from the elastic aorta. The most striking differences are: first, the shape of the aortic diagram remains the same whether the smooth muscles are contracted or relaxed; second, the hysteresis of the elastic vessels is smaller than that of the muscular vessels. This indicates that the arrangement of the different wall elements must differ in the two types of vessels. The smooth muscles, which play only a minor role in the elastic vessels, take a major one in the stretch curve of muscular vessels. Wezler & Schlüter (100) have designed a model which may give the action of the three wall elements and in

different contracted states. This model is shown (simplified) in figure 13. It is distinguished from the model in figure 9 by the parallel arrangement of the smooth muscles to the other elements. Sections 1 through 3 represent, as in figure 9, different stretch phases. The stretch takes place in the vertical direction. The element *a* represents an elastic fiber, the two elements *b* are smooth muscles, where the individual muscle fibers are in series, and element *c* is a collagen fiber. Both the elastic and the collagen fibers are wavy (unstressed) in phase 1. At the beginning of the stretch, near zero pressure, only the smooth muscles bear the stress. If the muscle fibers are contracted the slope of the pressure-volume diagram will be steep in the beginning and concave to the volume abscissa. Since the contracted smooth muscles behave in general like a visco-elastic material, the pressure-volume diagram will show prominent hysteresis as described in figure 2*b*. If the muscle fibers are relaxed, the slope of the pressure-volume diagram will be flatter. As extension proceeds, phase 2 will be reached, in which the elastic fibers are straightened. This will be at a higher pressure if the muscles are contracted than if they are relaxed. Finally, the collagen fibers are involved in the stretch (phase 3). If the smooth muscles are in strong contraction, the whole diagram within physiological pressure limits is concave to the volume abscissa. If the contraction is less, the elastic and collagen fibers come into play at lower pressures and the pressure-volume diagram shows an inflexion point and an S-shape. The pressure at which the inflexion point is located depends on the intensity of the contraction. If the smooth muscles are relaxed, the vessels will show in the beginning only a plastic elongation without a rise of pressure, but the pressure will increase when the elastic and collagen fibers are involved in the extension. The pressure-volume diagram is, from the very beginning, convex to the abscissa. The collagen fibers

serve as a "jacket" just as they do in the elastic vessels. They provide a safety factor to prevent overstretching the smooth muscles.

The model of figure 13 gives only the arrangement of the ring muscles in relation to the other elements. The more centrally the arteries of the muscular type are located, the greater is their amount of tension muscles [Benninghoff (10, 11)]. We must then assume a mixture of models shown in figures 9 and 13. The change over from the pure elastic-type model (fig. 9) to the pure muscular-type model (fig. 13) is gradual. The different behavior of the arteries may be the reason why different authors have different opinions about the architecture of the same wall. For instance Burton (20) suggests an arrangement similar to figure 9, whereas Bergel (12, 13) speaks of an arrangement similar to figure 13. Both may be right.

The smooth muscles in the muscular arteries are, during life, under a continuous stress since they are in parallel. Therefore they must have a certain basic tone to withstand the stress of the blood pressure. There is strong evidence that this basic tone may derive from myogenic activity. Bayliss (9) suggested, in 1902, that the blood pressure might act as a mechanical stimulus to the vascular wall. Lately it has become more and more evident that the smooth muscle possesses the capability of spontaneous activity (see above). For instance, denervated intestinal smooth muscles respond to a stretch with a contraction (fig. 4). The tonus of the vascular smooth muscles may be assumed to depend on the tension of the wall and consequently on the pressure within the vessel. Folkow (26), Thurau & Kramer (91), and earlier workers have found that the blood flow becomes constant above a certain pressure which may mean that the pressure or, rather, the wall tension serves as a stimulus for contraction of the smooth muscles, and so causes an increase in the peripheral resistance (see above). This autoregulation of flow results in a homeostasis of wall tension for, in contracting, the smooth muscles increase the thickness of the wall and reduce the radius of the lumen. Both of these changes reduce tension on individual muscle fibers. So the vascular smooth muscles may keep their tension near a constant level by contraction, when the pressure rises.

The suggestion has been made that basal tone may derive from locally released constrictor agents or regional reflex arcs of independent nerve plexuses in the vascular wall. However, Folkow & Öberg (29) have recently published experiments which eliminate these possible mechanisms. These experiments show

that the basic tone of precapillary resistance vessels and autoregulation of flow is not due to nerve plexuses or vasoconstrictor agents, but to myogenic activity. The task of the autonomic nervous system, which innervates the vascular muscles, would then be to control the myogenic activity and adjust it to the appropriate situation of the circulatory system (see above). In the same way tone may be controlled by chemical agents. This matter is also discussed in Chapter 37.

As the pressure perfusing a vascular bed is gradually reduced, the flow becomes less in proportion, the exact nature of this relation changing under different circumstances and with various vascular beds, as discussed in Chapter 28. The flow stops before the arteriovenous pressure difference reaches zero. The pressure at which this stoppage occurs has been called the "critical closing pressure" by Burton (19). The physical and physiological factors which determine the height of this pressure are discussed in Chapter 6.

Capillaries and Arteriovenous Anastomoses

The arterial side of the circulatory system is connected with the venous side by two types of vessels: capillaries and arteriovenous anastomoses (see also Chapter 27).

Capillaries are the tiny vessels through the walls of which materials are exchanged between blood and the tissues. They consist of a thin layer of endothelial cells, which sit on a basal membrane. On the outside of the capillaries are found the pericytes, which are cells with many irregular branches. Capillaries have no smooth muscles and, in spite of earlier contentions to the contrary, it is the current consensus that the pericytes cannot constrict mammalian capillaries (see Chapter 27); nor can the swelling of endothelial cells cause stoppage of flow [for additional references see Illig (41)].

The arteriovenous anastomoses are vessels the walls of which consist almost entirely of smooth muscle. They serve as a direct connection between the arteries and veins, bypassing the capillaries. The large amount of smooth muscle enables the arteriovenous anastomoses to keep their lumens closed over long periods of time. It is not impossible that these anastomoses regulate the capillary blood flow through the several organs, according to their activity. If an organ is active the anastomoses close and the blood may flow through the capillaries, whereas in a resting

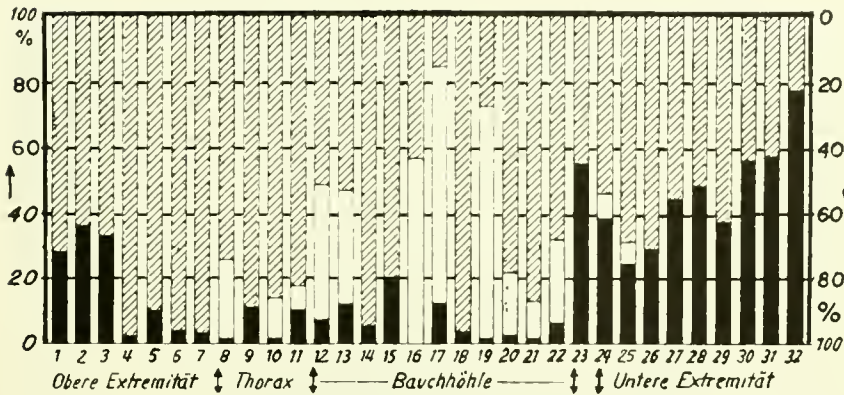


FIG. 14. Percentage of transverse (circular) muscles (black columns), longitudinal muscles (white columns), and collagen and elastic tissue (hatched columns) of the human veins at different sites. 1: Skin vein of the forearm; 2: v. mediana cubiti; 3: v. basilica; 4: v. comitans of the a. brachialis; 5: v. brachialis, proximal part; 6: v. comitans of the a. circumflexa humeri dorsalis; 7: v. axillaris; 8: v. brachiocephalica dextra; 9: v. thoracica interna; 10: v. thoracica longitudinalis dextra; 11: v. cava cranialis; 12: v. cava caudalis; 13: v. portae; 14: v. coronaria ventriculi; 15: v. lienalis; 16: v. renalis sinistra; 17: v. renalis dextra; 18: v. mesenterica caudalis; 19: v. cava caudalis, most distal part; 20: v. spermatica; 21: v. iliaca communis sinistra; 22: v. iliaca communis dextra; 23: v. dorsalis penis subcutanea; 24: v. saphena magna of the thigh; 25: v. femoralis; 26: v. poplitea; 27: v. saphena of the shank; 28: v. comitans of the a. tibialis posterior; 29: v. comitans of the a. tibialis anterior; 30: v. comitans of the a. dorsalis pedis; 31: skin vein of the back of the foot; 32: v. comitans of the a. plantaris fibularis. [v. Kügelgen (48).]

organ, the anastomoses may open and let the blood bypass the capillaries.

Anastomoses in the lung possess longitudinal muscles. Weibel (96, 97) has demonstrated that these muscles always appear in those vessels which have to withstand longitudinal elongation. He assumes that the longitudinal muscles support this stretch.

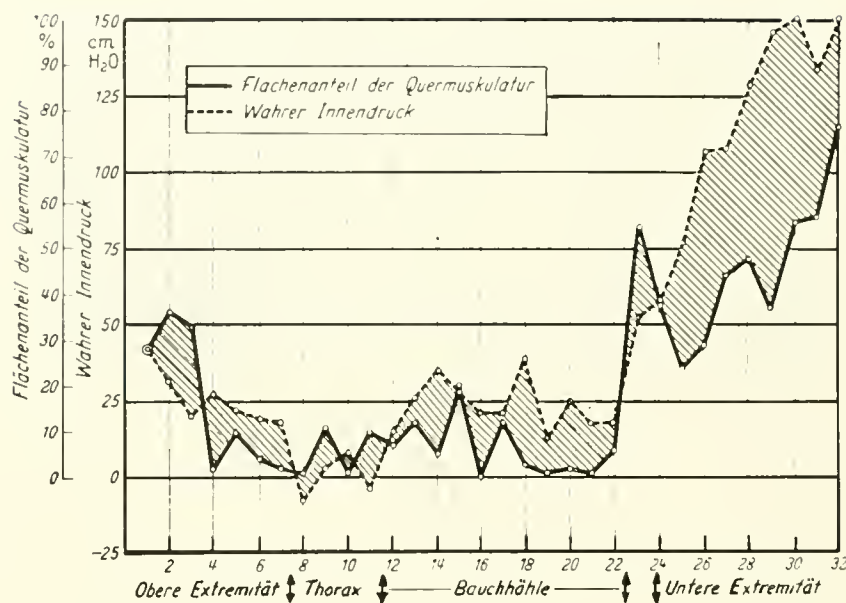
Veins

The veins, in contrast to the arteries, are very variable in their wall structure. Usually they have a larger percentage of collagen fibers than the arteries, but there are veins in which the muscular mass exceeds by far that of the collagen fibers. Veins have little elastic tissue (fig. 1). The arrangement of the wall elements is both circular and longitudinal in varying proportions in different veins. Tension muscles seen attached to elastic fibers in arteries seldom appear in veins. Grau (34) described elastic-muscular systems in the large veins of the cow, similar to the tension muscles described by Benninghoff (10, 11). However, v. Kügelgen (47, 49) could never find such tension muscles in human veins. He described, rather, muscles like the arterial ring muscles, the individual muscle cells being connected together as a network. This network of smooth muscles is tied to the collagen fibers and the intima.

Figure 14 shows the percentages of smooth muscles and collagen and elastic fibers in different human veins. The smooth muscles are separately graphed as transverse (circular) and longitudinal muscles. The longitudinal muscles of the veins are not arranged in bundles in the intima, as are those of the arteries. Rather, they form a network in the wall with the circular muscles, the smooth muscles being either longitudinal or transverse, or at any other angle.

The circular muscles are mainly in the veins of the leg, whereas the longitudinal muscles predominate in the abdominal veins. Figure 15 shows that the proportion of circular muscles parallels the pressure in the veins in the erect posture, there then being considerable hydrostatic pressure in the human leg veins. Since the wall tension in a tube, in the transverse direction, is twice that in the longitudinal direction [Frank (30)], the percentages of circular muscles are higher in veins subject to higher pressures. Hydrostatic pressure and wall tension vary with posture; therefore this variable pressure load can be supported better by muscles capable of myogenic activity, as in arteries, than by collagen or elastic tissues (see above). Along with the higher amount of smooth muscles in the leg veins the relationship of radius to wall thickness is less than that of other veins [v. Kügelgen (48)]. Veins of the thorax,

FIG. 15. The relationship of the abundance of transverse (circular) muscles in human veins (smooth line) to the venous pressure in the erect posture (dotted line). The numbers indicate the same veins as in fig. 14. [v. Kügelgen (48).]



abdomen, and neck are not under this hydrostatic stress and have less circular muscle tissue.

The mechanical properties of the veins are similar to those of the arteries. Smaller veins show different pressure-volume diagrams, depending upon the state of contraction of their smooth muscles, as do those of muscular arteries [Alexander (2)]. The only difference between the diagrams of the muscular arteries and the veins is that the diagram of the veins is located at much lower pressures. This indicates that the elasticity of small veins depends to a high degree on smooth muscle. The large veins, like the vena cava, give a pressure-volume diagram more like that of elastic arteries [Blömer (14)]. It shows an S-shape, like the aorta, with an inflexion point at the low pressure of about 7 mm Hg. This S-shape does not depend on the activity of the smooth muscles. The main support of the wall tension of the large veins, at least above 7 mm Hg, is the collagen tissue rather than the elastic tissue, as is the case for elastic arteries, since the amount of collagen exceeds by far the amount of elastic tissue in the vein wall. The relatively high distensibility of the vena cava, in spite of the collagen fibers, may depend on a gradual recruitment of these fibers, as shown in figure 9, phases 3 and 4, or it may be due to a reorientation of the network formed by the collagen fibers in the venous wall [see v. Kügelgen (49)].

The most striking difference between arteries and veins are that the veins possess valves and are securely embedded in the surrounding tissue (33, 51, 53, 78),

whereas the arteries never have valves and they are loosely connected with the surrounding tissue.

The valves of the veins are folds of the intima. They consist of collagen and elastic fibers but not of smooth muscles. Around the vein at the base of the valve is a thickened band of collagen fiber (51). Usually two valves face each other [Bardeleben (8)]. The leg veins are best guarded by valves. Very small veins are said to be free of valves [Klotz (45)], as are the venae cavae. The valves minimize postural hydrostatic pressure changes in the leg veins, protecting the capillaries and the veins themselves from unphysiological pressures.

The action of the skeletal muscles, compressing, stretching, and releasing the veins, and even arterial pulsation (53, 78), cause periodic changes in venous capacity. Since the valves open toward the heart, these movements cause the veins to act as pumps, promoting return of blood to the heart and maintaining low capillary pressures (for further details see Chapter 32).

The numbers of valves in the veins depend very much on the age of the individual. Many valves degenerate with aging. Bardeleben (8) has ascertained, for example, that the greater saphenous vein of a child has, on the average, 13.6 valves, whereas that of an adult has only 10.7 valves. Klotz (45) has even found up to 70 per cent of atrophied valves at age 70. The first sign of degeneration is a functional insufficiency of the valves permitting leaking at higher pressures when the vein is distended, although they

still are tight at low pressures [Schlüter (79)]. Further degeneration makes them leaky at low pressures and later they are so degenerated that only a small margin remains or the valve leaflets are broken through. At last they vanish completely. The effects of venous valvular insufficiency are discussed in Chapter 36.

The firm anchorage of the proximal part of the veins may facilitate transmission of arterial pulsation from arteries to their venae comitantes [Schade (78), v. Lanz *et al.* (53)], but it seems also very convenient for another task. Any distensible tube which stands upright and is filled with fluid tends to pull downward. The radius in the proximal part is then small and the wall is stretched mainly in a longitudinal direction. It is therefore necessary that the tube be supported in the proximal part in the longitudinal direction and be fixed to its surroundings. Such a support may be formed in the veins by the bracing straps (33, 53) and also by the longitudinal muscles. In the distal part of such an upright tube the radius is enlarged and the wall is stretched mainly in a transverse direction. As indicated above, this is countered by the increasing amount of circular muscles.

NUTRITION OF THE VASCULAR WALL

The vascular wall is a living organ and its smooth muscles need a source of energy. Their nutrition is accomplished by two different means: diffusion from the circulating blood from the inside of the vessel toward the outside, and from the vasa vasorum vessels which dip into the vascular wall from the outside. These two supply routes meet in the vascular wall. Müller (64) has demonstrated a model in which ten coaxial thin rubber tubes with increasing diameters were telescoped and fixed so that the fluid between the different sheets could not escape during distention. This model satisfies very well the situation in the vascular wall, which is also built from different layers consisting of different materials. The pressure between the sheets is equal to the negative radial stress, and the tension of the different sheets of the model decreases nearly linearly from the inside to the outside at any given internal pressure. The innermost sheet has almost the same pressure as the filling fluid, whereas the outermost sheet is at the ambient pressure. This means that the vessels which supply the vascular wall meet progressively higher pressures the further they penetrate the wall. On the other

hand, the pressure gradient from the inside toward the outside facilitates the movement of materials directly from the circulating blood through the wall. The border between diffusion and vascular supply in the vascular wall depends on the thickness of the wall. The limit for diffusion is set by oxygen, which is transported in the blood by the hemoglobin and which can supply tissues adequately if the distance from the hemoglobin, which stays in the blood, to the tissue cells is not too great. This distance is, in the vascular wall, about 500 μ [Linzbach (56)]. The limit for the vasa vasorum is set by the pressure in the wall. Since the vasa vasorum come mostly from the adventitia, the pressure fall over the length of the vasa vasorum allows them only to penetrate as far as the pressure in the wall is less than the pressure of the intramural capillaries.

Diffusion from the Inside

The whole circulatory system is lined with a single layer of endothelium. This lining prevents extravasation of blood even if the pressure in the vessels exceeds by far the surrounding pressure. Any nutrient material entering the vascular wall from the inside must pass across this endothelial lining. Such penetration is rendered possible either through the pressure and concentration gradient between the blood and the wall tissue or by means of active transport. Chambers & Zweifach (21) assume that the individual endothelial cells are held together by a cement substance and that this cement substance makes penetration possible. However, Linzbach (56) could never find such a cement substance. He describes cell branches which are near the basal side of the endothelial cells, and with which the endothelial cells are very tightly connected. The boundary between the cells may form fissures, where capillary attraction may be effective and render penetration possible. Pappenheimer (65) suggests channels between the endothelial cells with a diameter of 30 to 45 A, through which the materials can enter the wall. All these mechanisms depend on a pressure gradient between the blood and the wall tissue or an osmotic concentration gradient of the different materials.

However, there may also be active transport. Moore & Ruska (63) described small vacuoles on the surface of the endothelial cells which contain blood plasma. These vacuoles separate themselves from the surface and wander through the cell sub-

FIG. 16. Vasa vasorum in the wall of the aorta of the horse. China ink, thick cuts. *Left*: longitudinal section; *right*: cross section. [Straubesand (87).]

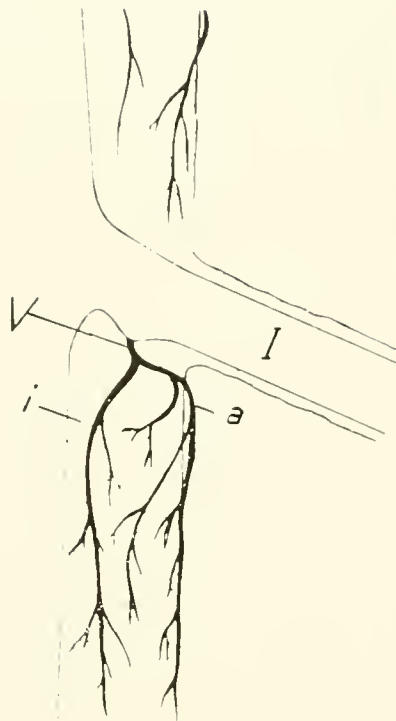
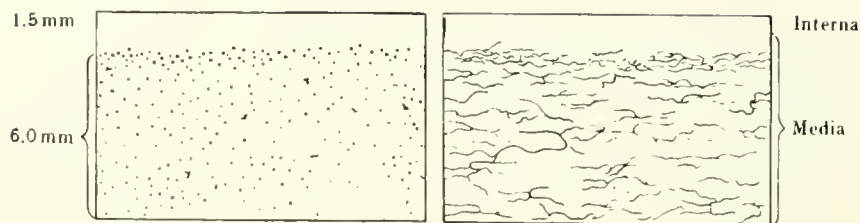


FIG. 17. Schematic longitudinal section through the aortic wall at the origin of an intercostal artery. *I* = intercostal artery; *V* = vas vasis externum; *a* = outer branch; *i* = inner branch. [Schönenberger & Müller (82).]

stance to the basal side of the endothelial cells, where they release their contents to the wall tissue. This transport is called cytopempsis. Another possibility of active transport through the endothelium may be by a similar mechanism which was described by Ussing (92) for the frog skin. He demonstrated that sodium is actively transported across the skin cells by a carrier system located in the cell membrane. This would mean that ions or other materials enter the endothelial cell passively through the surface membrane, along a concentration gradient, and are then actively transported out of the cell and into the wall tissue against a concentration gradient. Sawyer & Valmont (77) have published evidence for such a mechanism in the canine thoracic aorta and vena cava, where the net flux of sodium or chloride ions



FIG. 18. Cross section through the thoracic aorta of the dog, showing a vas vasis internum. There is no branching of capillaries in the intima and the innermost part of the media. The dark masses in the outer third of the media are accumulations of injected material that has broken out of the capillaries. [Woerner (101).]

in the aorta is from the inside to the outside. In the vena cava it is in the opposite direction (for a possible explanation of this contrasting behavior see below). The variety of theories about the transport of material across the endothelial lining shows that much work remains to be done. Most of these theories are deduced from experimental results on capillary endothelial cells but it may be that transport differs in the capillary endothelium and the endothelium of larger vessels. There is also the possibility that different tissues use different transport mechanisms. (See also Chapter 29.)

The further transport through the intima and the media may be passive in the intercellular space,

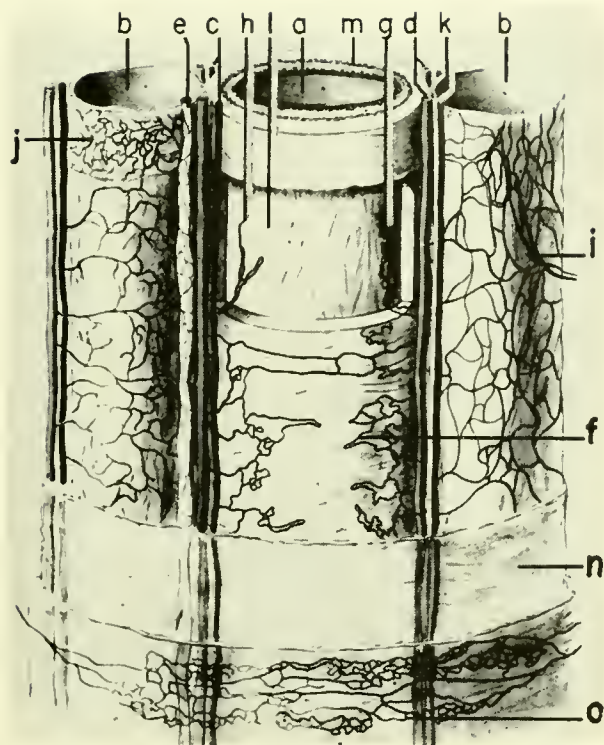


FIG. 19. Schematic drawing of the vascularization of a middle-sized artery with both its venae comitantes. *a*: Artery; *b*: venae comitantes; *c*: arterial vasa vasorum; *d*: venous vasa vasorum; *e*: lymphatic vessel; *f*: capillaries of the arterial sheath; *g*: capillaries in the stratum longitudinale fibroelasticum of the artery = wall capillaries; *h*: small channel, less than $3\ \mu$ thick; *i*: vascular network in the venous wall; *j*: capillary network in the venous wall; *k*: nerve; *l*: stratum longitudinale fibroelasticum = adventitia of the artery; *m*: media of the artery; *n*: circular sheath of the vessel group; *o*: conjunctiva of the sheath. [Lang (51).]

effected by the pressure and concentration gradient across the vascular wall.

Vasa Vasorum

The vasa vasorum penetrate the vessel wall to different depths, depending on the thickness of the wall and the type of vessel. The thicker the wall, the greater the part of the wall tissue they supply. In general, veins have greater vascularization than arteries. The vasa vasorum penetrate the aortic wall as far as the inner third of the media (fig. 16). The innermost part of the media and the intima are always free of capillaries. Only arteriosclerotic vessels with a thickened intima show vascularization of the innermost part of the wall [Woerner (101)].

The vasa vasorum of the aorta can be classified as vasa vasorum externa and vasa vasorum interna. The vasa vasorum externa originate near the origin

of arterial branches, such as the intercostal arteries. They soon divide into an outer branch and an inner branch (fig. 17). The outer branch goes into the adventitia and from there sends branches into the wall, whereas the inner branches remain within the wall. Their branching is mostly trichotomous. The vasa vasorum interna originate directly from the lumen (fig. 18) far away from branching vessels, that is, in the aorta on the ventral side [Schönenberger & Müller (82)]. They are not very numerous; according to Woerner (101), there are never more than two per square centimeter. They are mostly found in the proximal part of the aorta and very seldom in the distal part. The vasa vasorum externa and interna anastomose in the aortic wall. The vasa vasorum externa are about 65 to 70 mm in length, the vasa vasorum interna about 30 to 50 mm.

The more peripherally the arteries are located, the less vascularized is their wall. Figure 19 shows a schematic drawing of an artery with its two venae comitantes from a human shank. The vasa vasorum of the peripheral arteries arise at smaller branches of the artery, similar to the vasa vasorum externa of the aorta. There are no vasa vasorum interna in these arteries. The vasa vasorum never dip into the media. They are located in the stratum longitudinale fibroelasticum, the innermost part of the adventitia. They form their capillary loops mostly in the longitudinal direction. In addition to these capillary loops there are still smaller vessels. Lang (51) has described two types of such small vessels. The first type is a small, blind-ending channel about 3 mm in length and 1 to $3\ \mu$ diameter (fig. 19) which is much too small for blood cells to pass. These small channels run into the tip or the venous part of the capillary loop. The second type is a network of small channels of about the same diameter (fig. 20).

The same vas vasis which supplies the artery also supplies its venae comitantes (fig. 19). In contrast to the case for arteries, the capillaries in the venous wall form a dense network which extends to the media. The segment around the valves is usually not vascularized. The venous vasa vasorum do not drain directly into the large vein along which they lie; rather they and their counterparts in the arterial wall drain into a small venous branch [Lang (51)].

Schönenberger & Müller (82) have calculated the drop of pressure in the vasa vasorum externa of the aorta, finding that the capillary pressure within the wall can be sufficiently high only if the origin of the main vas vasis is very near the inner surface of the aortic wall (fig. 17). The intramural capillaries must be quite near to the origin of the vasa vasorum externa

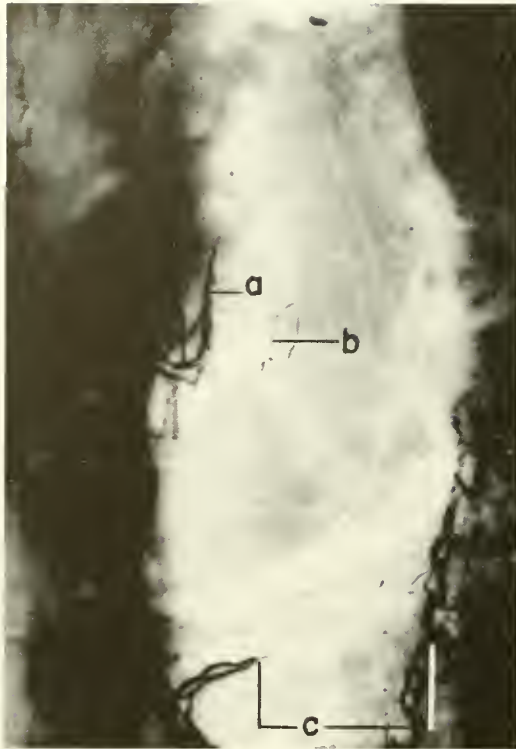


FIG. 20. Net-shaped small channels with a diameter of $1-2\ \mu$ in the adventitia of the peroneal artery. Capillaries of the sheath and the arterial sheath partly removed. The small channels were connected with the capillaries of the sheath. *a*: Wall capillaries in the stratum longitudinale fibroelasticum; *b*: network of small channels; *c*: arterial sheath and capillaries of the sheath, in situ. [Lang (51).]

to maintain a pressure which is necessary to exceed the tissue pressure. If the capillaries are too far from the origin, the pressure will be too low to supply the wall efficiently. At greater distances from the intercostal arteries, the vasa vasorum interna, with their short delivery system, may provide sufficient blood supply.

Schönenberger & Müller (82) have also determined the flow and resistance in the vasa vasorum of the cow's aorta. Flow increases and resistance decreases, with rising pressure, with a maximum at

about 140 mm Hg (distended vessels). At higher pressures, a decrease of flow and an increase of resistance occurs (collapsed vessels). The maximal flow seems to occur at the systolic blood pressure level. This indicates that nutrition of the vascular wall may be problematic in hypertension, if the diastolic pressure exceeds the physiological systolic pressure, since the flow in the vasa vasorum may never reach the maximum. The inner region of the wall, which is not nourished by the vasa vasorum, also suffers ischemic changes, including a compensating increase in vascularity.

The lymphatics certainly play no role in the circulation of the tissue fluid within the vessel wall itself, as they do in other organs. The very small channels which arise from capillaries (see above) and which have a diameter of 1 to $3\ \mu$ may function like the lymphatics with local drainage (51). The mechanical or hydrostatic pressure gradients are irrelevant to this diffusion transport and determine only the direction of flow in the vasculature of the vessel wall—whether the supply to a capillary comes from an internal or an external arterial branch.

The situation in the veins is quite different from that in the arteries. There are no channels of supply from the lumen of the vein as is the case in the artery and, since the venous blood is depleted of oxygen and nutrients, the supply by diffusion through the intima is nonexistent or very limited. The pressure gradient is from the external arterial plexus to the capillary plexus, extending as far as the intima. Venous drainage is into small venae vasorum rather than into the lumen of the large vein. The interstitial space is probably drained by "lymphatics", although the fluid may pass directly across the intima and into the lumen. The pressure gradient is favorable for this movement of fluid and it might nourish the non-vascular inner wall. This concept agrees very well with the experiments of Sawyer & Valmont (77), who have found a net transport of Na and Cl from the outside to the inside in the canine vena cava.

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Patterns of the arteriovenous pathways

MARY P. WIEDEMAN

*Department of Physiology, Temple University
School of Medicine, Philadelphia, Pennsylvania*

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Summary

ALTHOUGH CAPILLARY VESSELS in living animals have been observed microscopically for three hundred years, there is a great diversity of opinion regarding the structure and function of minute vessels in terminal vascular beds. Actually, a survey of the descriptions of patterns formed by capillary networks and the flow of blood through them in a wide variety of tissues and organs reveals great similarity in vascular patterns and also in the manner in which blood flows

from arterioles through capillary nets on to collecting venules. This similarity of structure and function leaves the impression that acceptable generalizations, applicable to these terminal beds, must be developed in order that future studies may prove profitable.

It is well known that unnecessary disagreement arises from lack of uniformity in terminology. It is equally obvious that unnecessary confusion arises from assigning complex functions to isolated components of a specific vascular bed when, in truth, both the activity and the structure are common features of small blood vessels anywhere.

DEFINITIONS

Any attempt to supply a list of universally acceptable definitions of vascular structures would be useless, and yet it is necessary to present some generalizations regarding current usage of terms before describing the types and variations of structural patterns that connect distributing arteries and collecting veins.

The term "microcirculation" is used to designate blood flow through small vessels at the capillary level (48). The microcirculatory bed is the ultimate portion of the cardiovascular system which is generally accepted as being concerned with the transfer of gases and nutrients and the removal of metabolic waste products. Minute precapillary arterioles and postcapillary venules are included with the capillaries as major components of the microcirculation (53).

Terminal arterioles are the final arterial ramifications, the branchings of which continue as non-muscular capillary vessels (88). They are further

defined (152) as vessels which have a single layer of smooth muscle and very little supporting connective tissue. The "metarteriole," a term introduced by Chambers & Zweifach (20), is defined by Zweifach (148) as a primary structural unit which serves as a framework for the distribution of capillaries.

The term "precapillary sphincter" was first used by Chambers & Zweifach (20) to designate the muscular investment at the origin of the outflowing branches of the preferential channel (distal continuations of arterial vessels that go directly to the venous side). These outflowing branches lead into true capillaries. In more general usage, a precapillary sphincter is the last smooth muscle cell along any branch of a terminal arteriole (130).

A capillary may most simply be described as an endothelial tube devoid of smooth muscle and having a minimal amount of supporting elements (48). In descriptions of vascular patterns and flow it is not necessary to add any qualifications as to size, direction of flow, or function.

Venules originate at the appearance of the first smooth muscle cell on a postcapillary vessel. Venules merge into veins which have a double coat of circular and longitudinal muscle cells.

Vasoconstriction is the contraction of the smooth muscle of the vessel wall, vasodilation is relaxation of the smooth muscle. Vasomotion refers to any active change in the diameter of blood vessels (81, 89).

There are numerous other designations for vascular structures, unique to specific organs or tissues, which will be discussed where they appear in the descriptions of arteriovenous pathways in various sites.

TECHNIQUES FOR MICROSCOPIC OBSERVATION OF SMALL BLOOD VESSELS

In discussing the techniques used for microscopic observation of small blood vessels, the most commonly used sites and methods have been included. There are numerous adaptations of the basic techniques for specific approaches, and also many highly specialized adaptations for specific areas that will be described in sections of this chapter where they are pertinent.

In general, there are four basic methods: 1) observation of tissues and organs *in situ* illuminated by the fused quartz rod, 2) exteriorization of internal tissues or organs which can be spread out as a thin layer for examination, 3) preparation of tissues using transparent chambers, 4) utilization of superficial structures which can be seen with direct or transmitted light.

The brevity of the descriptive material should not mislead the reader as to the difficulty of mastering the technical problems associated with each method, nor should he overlook the necessity of being completely familiar with the characteristics of the site selected for observation. A survey of the methods should make it clear that some sites or structures are more suitable than others for any specific investigation and should be evaluated on that basis.

Hamster Cheek Pouch

A method for observation of peripheral circulation at the microscopic level in the membranous cheek pouch of the hamster has been developed by Fulton, Jackson, and Lutz (51, 52, 80). The cheek pouch of the anesthetized hamster is everted and, when properly exposed for viewing, forms a flat double-layered preparation suitable for low power magnification. The pouch is bathed in a 37°C Ringer's solution. If higher magnifications (200× to 1200×) are used, it is necessary to cut through the upper layer to form a flap of a single layer. The originators of the method believe that the cheek pouch is ideally suited for investigations on small blood vessels because the thin membrane presents a normal physiological surface with blood vessels in their usual tissue environment. A valuable feature of the pouch is also that the same natural vascular bed can be studied over long periods and thus changes in circulation or other characteristics, such as growth of vessels, can be followed. The pouch is more vascular than the mesentery of rats or membranes in transparent chambers. Its vascularity makes tumor transplantation extremely successful. Other investigations made on the hamster cheek pouch include the study of blood pressure, inflammation, hemostasis, petechial formation, thromboembolism, bacterial and parasitic infections, drugs, and the vascularization of tumor transplants.

The disadvantages of the preparation are that the animal is anesthetized, the exposed tissue must be irrigated and kept at body temperature, and for high magnifications the integrity of the vascular bed is disrupted by surgery needed to obtain a single-layered membrane. The membranous surface continuously exudes mucus, which reduces visibility of the underlying structures. In the hands of its originators, judging by their excellent films, the method is very satisfactory for the investigations in which it has been used.

Transparent Chamber

The development of the transparent chamber technique and its utilization in numerous tissues have been extensively reviewed recently (3, 24, 25). For a detailed description of the methods for installation and observation, the reader may refer to these papers.

Basically, the method consists of the insertion of a glass and mica chamber fastened to the cartilage of the rabbit ear or other applicable site. Since the first chamber was designed by Sandison (104) in 1924, several types have evolved, with modifications and improvements introduced for specific purposes. The round-table chamber, essentially the same as the original Sandison model, was introduced in 1930 by Clark *et al.* (36). The chamber is constructed to allow new tissue to grow into an empty space from the edges of cartilage left by a punctured hole. This chamber has been used to study the growth and development of blood vessels, lymphatics, and nerves. The preformed tissue chamber (36) is one in which the original tissues can be observed after removal of the cartilage and skin of the inner side of the ear. The moat chamber was developed to study the response of the vessels to various chemical substances (1, 2). It contains a small space or moat to permit injection and withdrawal of fluids. The chamber has been used to investigate absorption, diffusion, and the reactions of vessels to chemical solutions. A removable-top chamber was designed by Williams (138) for the purpose of obtaining easy access to living tissue of the chamber for transplantation of organs or tissues. The most recent improvements have been developed by Williams & Roberts (140), who designed a versatile and highly useful chamber which has the following characteristics: it has a longer life than any other type of chamber, produces very little irritation to the ear, is quickly and easily installed, can be used for transplants of tissue, may be modified to study existing or preformed vessels, and may be adapted for the introduction or removal of fluids. Epidermis, which invades the round-table chamber, is never seen to grow into this new tantalum and mica chamber.

Clark (25) points out the many advantages of the transparent chambers, among them the fact that the manner of growth and extension of capillaries, the growth of nerves along arterioles, and the development of inflammatory reactions can be observed for long periods of time in unanesthetized animals. The disadvantages include injury to the nerves during installation, the rigidity of the chamber which may

result in an abnormally high external pressure, especially with inflammation, and the occurrence of infection. The advantage of having an unanesthetized animal is great, and equally helpful is the fact that the exposed tissues need not be warmed or irrigated as is the case for visceral or other exteriorized tissues. A serious disadvantage of the technique is the disruption of normal circulatory patterns and behavior by installation of the chamber in which the new tissue must form.

Fused Quartz Rod

A lengthy discussion of this method of transillumination of living internal organs in situ for microscopic study is given by Knisely (70). The limitations and the applications of the method are fully covered.

The method is based on conducting intense light to the structure to be studied by a fused quartz rod. These rods conduct light around bends and turns by internal reflection. Overheating and drying of the tissue is prevented by an isotonic wash solution. Magnifications from 20 times to 1000 times can be used.

Transillumination with the fused quartz rod has been carried out in a wide variety of tissues including frog skin, tongue, brain, gastrointestinal tract, stomach, bladder, striated muscle, lung, kidney, and liver. In mammals, the small vessels in smooth muscle, mesentery, uterus, spleen, and liver have been studied.

Knisely feels that the limitations of the method include the necessity for an anesthetic, surgery, and the exposure of internal organs to the air. The method is best used to examine structures at their natural anatomical surfaces or free edges rather than at cut surfaces. In examining a thick organ, such as liver or spleen, one is limited in the degree of magnification of the deeper structures due to the direct relationship between the focal length and magnifying power of lenses. Fulton (49) points out that this procedure does not reveal certain details of vascular structure or permit critical discernment of individually formed elements. It remains, however, the only method applicable to many types of tissues, but requires rational selection of the problems to be studied.

Bulbar Conjunctiva

Although observations of the conjunctival vessels are not new, recent improvements in microscopes and

lights have made this site a popular one, especially for observing changes in vascular patterns and flow in diseases in humans. Specific instructions for its use can be found in papers by Bloch (15), Grafflin & Corddry (56), and Lee (76).

The type of microscopic and lighting equipment, as well as the position of the patient (supine or upright), varies with the investigator, but, generally, compound microscopes, routine ophthalmological supports, and lights of moderate intensity constitute the basic components.

Bloch (13) notes that the walls of the blood vessels are not clearly seen because of the use of oblique illumination, although a moving column of blood can be clearly seen against the white background of the sclera. Other limitations are that optical resolution is lost by the patient's inability to hold the eye still, edema, highlights due to lacrimation, and excessive abnormal pigmentation in some cases. Very high magnification is difficult because of movements of the eyeball and the inability of the patient to tolerate light of high intensity. Also, high power objectives must be too close to the eyeball if they are to be in focus.

The advantages of the technique are that blood vessels in an unanesthetized human can be readily observed without any surgical intervention or any preparation to render the vascular beds visible. Tears supply the proper irrigation for this membranous tissue. An entire vascular field can be studied again and again in the same subject, and blood flow can be followed from arteriole through capillary to venule.

Rat Mesoappendix

The technique for microscopic observation of mesenteric structures, as described in detail by Zweifach (145), has been used by him in studies on dog omentum and mesenteric structures in several animals, but primarily in the cecal mesentery (mesocecum) of the rat.

Preparation of this tissue consists of exteriorizing the cecum of the anesthetized rat and then spreading the mesentery, which lies between the cecum and the terminal ileum, for observation. The mesentery is continuously irrigated with a warm Ringer's gelatin solution.

Zweifach (147) believes that the advantages of using this terminal vascular bed are: *a*) the accessibility of the vessels for direct stimulation by mechanical, chemical, or electrical means; *b*) clarity of visualiza-

tion; *c*) minimum interference by surgical procedures to normal vascular behavior; *d*) adequate display of the entire extent of the terminal vascular bed.

The disadvantages include those which apply to any technique using anesthetized animals subjected to surgical procedures to expose the tissue for observation. An idea of the lability of this vascular bed may be obtained by reading the precautions to be taken in using the rat mesoappendix for bioassay (153).

Bat Wing

Microscopic observations of vascular structures in the bat wing, a comparatively old technique (68), was revived by Nicoll & Webb (88) in 1946. A description of the preparation and current uses may be found in papers by Webb & Nicoll (130) and Wiedeman (136).

An unanesthetized animal is slipped into a holder that allows the wings, lightly held by spring clips, to be extended over a glass plate. Magnifications up to 2500 times can be used with good resolution.

The simplicity of the preparation is one of its great advantages, coupled with the elimination of anesthesia and surgery which permits observation without disturbing the normal circulation or subjecting the animal to undue stress. The blood vessels and lymphatics are accessible for cannulation which permits perfusion of drugs or measurements of pressure, and the nerves can be readily stimulated or sectioned. Also, in this mammal the two wings can be used simultaneously, which allows one for control and the other for experimental procedures.

One undesirable feature is the difficulty in obtaining bats during the entire year, and, because the animals will not eat in captivity, their survival time in the laboratory is limited to a few months. Also, histological sections are difficult to prepare for study because of the extreme thinness of the wing.

Utilization of these various techniques has resulted in the resolution of some old controversies, e.g., the role of the Rouget cell, and has clarified to some extent the anatomical structure and physiological function of terminal vascular beds. It has made many investigators aware of the danger of ascribing specific changes in blood pressure or the rate or volume of blood flow to the activity of small blood vessels, on the basis of indirect measurements. While the change in systemic pressure following some experimental procedure need not be challenged, the means by which it is brought about may be better explained

if direct observations of the vessels controlling peripheral resistance are employed.

STRUCTURE OF TERMINAL VASCULAR BEDS

From the foregoing section it is apparent that the microscopic blood vessels which connect the venous and arterial systems have been studied in a wide variety of tissues with equal variety in the choice of experimental animals. Differences in vascular patterns and structural components are to be expected, but these differences are minor compared to the more general similarities among the various microcirculatory beds. It is this aspect that will be emphasized in the following descriptions of the microcirculation.

Microcirculation in the Bat Wing

Utilization of the bat wing for studies of the structure and function of small blood vessels has a long history. An interesting and detailed report appeared in 1852, written by T. Wharton Jones (68), who described the impressive rhythmical vasomotion of the veins. Scattered publications by other investigators appeared (18, 63, 87) early in the twentieth century when new interest in capillary circulation was at its peak. The interest in the wing of the bat as a site for microscopic observation of vascular beds was stimulated in 1946, when Nicoll & Webb (88) published the results of several years of observations. A description of the vessels and their patterns in the terminal vascular beds of the wing follows.

The major site of peripheral resistance was found to be in the small arteries which anastomosed to make interconnected channels or loops. These small arteries, which arose from the main arterial plexus and formed arteriolar nets, had the capacity for changing their lumen size by vasoconstriction. The smaller arterioles of the nets usually had an inside diameter that was equal to or smaller than that of a red blood cell. Nonmuscular capillaries arose as branches of any of these vessels of the arteriolar plexus, the parent vessel of the nonmuscular capillary being designated the terminal arteriole. The muscular coat of the terminal arteriole became less regular as the vessels advanced peripherally, as did the number of muscle cells on the branches arising from it.

The pathways between the arteriolar and venous plexuses were seen to be similar to those of the rabbit ear, as described by Clark & Clark (34) and Sandison (106), with no preferential channel to carry blood

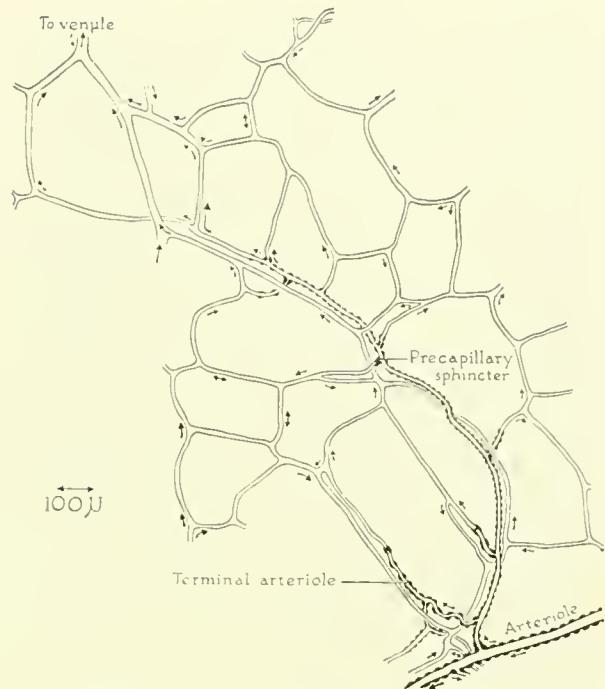


FIG. 1. Paths of blood flow in capillary bed in small area of the bat's wing. [From Nicoll & Webb (88).]

from the arterial to the venous side. Blood was seen to take alternate routes through the capillary nets. At times, especially in the terminal arterioles, there appeared to be a major path of flow through the capillary vessels to the venules, but this path was seen to be inconsistent and changed to alternate routes with modifications in arteriolar or venular circulation in adjacent regions (see fig. 1).

Supravital staining made it possible to study the arrangement of the vascular smooth muscle of the various vessels. Arteries had both circular and longitudinal muscle fibers, the latter disappearing in the arteriolar vessels. The terminal arteriole gradually lost its circular muscle investment until areas of bare endothelium could be seen and finally a single coiled muscle cell formed the precapillary sphincter. The spiral arrangement of a muscle fiber continued for a number of turns, presumably reaching a length of over 100 μ if uncoiled. Postcapillary vessels acquired a muscular coat in the region of the first valves, and thus veins were formed. Veins had the usual double layer of circular and longitudinal muscle fibers.

Because of the small caliber of arterioles and capillaries, flow was frequently seen to stop due to obstruction by a leukocyte. In some instances, an internal pressure increase would cause the leukocyte to move on. At other times, the leukocyte could be seen to

migrate slowly along the vessel wall until it reached a larger vessel where it was swept forward in the blood stream. Plugging of small vessels by leukocytes was found in normal fields with vigorous flow, and this obstruction determined to some extent the flow of blood through the capillary nets.

In 1954, Webb & Nicoll (130) discussed the angle which an arterial branch forms as it leaves its parent vessel. The downstream angle was found to approach 45 degrees. Webb and Nicoll postulate that this helps to insure almost equal pressure in the artery and the branch which arises from it. A similar type of branching is seen in the arcuate arrangement formed by arterioles. Arterioles, however, usually leave arteries at right angles. The arteriolar branches have sphincters at their point of origin that regulate the size of the lumen of the branching vessel as it leaves the artery.

The arcuate system formed by the arterioles affords collateral pathways and contributes to a uniform distribution of blood at uniform pressure within the capillaries.

The capillaries form an extensive anastomosing net which is supplied by terminal arterioles arranged in such a manner that no capillary net is very far away from its arteriolar supply.

Active vasomotion of arteriolar vessels is, according to Webb and Nicoll, the principal factor of a local nature that regulates blood flow and blood pressure in the capillary beds. The activity of the muscular wall of the arterioles, which constitutes active vasomotion, is independent of central nervous control. Degeneration of nerves supplying an area does not affect active vasomotion in the smaller arterioles, nor does stimulation of intact nerves, although this does result in a contractile response from the arteries or the larger arterioles.

Blood flow and blood pressure in capillary nets, then, are controlled by two factors, one being the anatomical arrangement of the arterioles which form arcades, and the second being the active vasomotion of the arterioles which is determined by local conditions.

Further discussion of the arcuate patterns formed by arterioles in the bat wing appeared in a report by Nicoll & Webb (89) in 1955. Arteriolar vessels form arcuate configurations. These anastomosing vessels are approximately equal in diameter. Several distinct arteriolar arcuate systems can be identified arising from either an artery or a large arteriole. Two characteristic features were found in the manner in

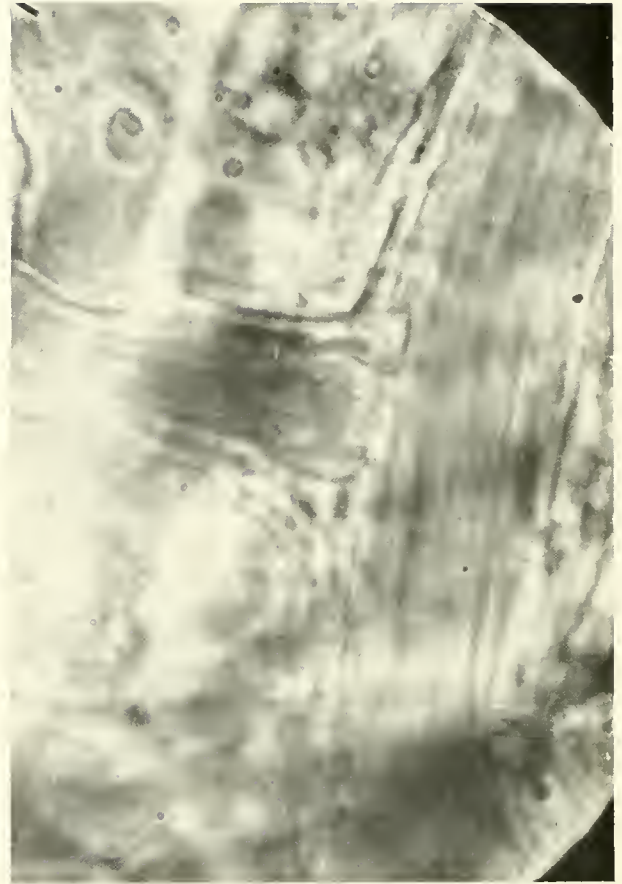


FIG. 2. Enlargement of an arteriolar branch at its point of origin. Bat wing. $\times 875$.

which the arcuate systems began. One was the angle of origin of the arteriolar vessels from the parent vessel, and this was found to be 90 degrees or less in reference to the forward direction of flow in the parent vessel. The second characteristic feature is a dilatation or enlargement of the arteriolar branch at its point of origin compared to its diameter throughout its length. Also, the inside diameter of the opening between the parent vessel and branch is much smaller than the average inside diameter of the branch (fig. 2). This formation, described by Nicoll and Webb in the bat wing and named "Indian Club," has not been described in microscopic vessels in other terminal vascular beds. In view of the fact that the notable appearance of the enlargement of a vessel at its junction depends to some degree on tonus, it may not be readily apparent in anesthetized animals in which vessel tone is low. If the tonus of the branch is quite low, there may be little or no apparent difference be-

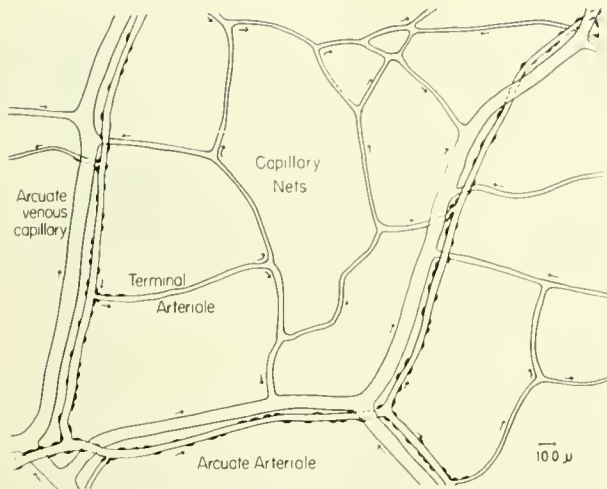


FIG. 3. Arcuate patterns in the terminal vascular bed. [From Nicoll & Webb (89).]

tween the outside diameter of the branch at its junction and along its length. Terminal arterioles originate mainly from the smallest arcuate vessels, but may also arise from any of the arcuate arterioles or a small artery (see fig. 3).

The capillaries form extensive nets, and the distribution of blood within the nets from any particular terminal arteriole is limited. Local conditions, which must be considered to be a major factor of control, constantly change the paths of blood flow through the capillary bed.

Venous vessels show an arcuate pattern that roughly follows that of the arteriolar vessels. At the point where a capillary vessel joins a venule, a valve may often be seen, although in many instances no such structure is evident. Nicoll and Webb suggest that since the muscular coat of the venule begins in the immediate vicinity of the valve, this site may be considered as the true junction between capillary and venule.

The flow of blood through the capillary nets is controlled chiefly by activity of the terminal vessels. When they are dilated, flow is rapid and continuous in the capillary nets. Constriction of a terminal arteriole necessarily stops the flow of blood through the capillary vessels supplied by it. When the numerous terminal arterioles which supply an interconnected network of capillary vessels are contracting and relaxing intermittently and aphasically, the flow of blood into collecting venules may be continuous. Cessation of flow from venous capillaries into venules is often produced when resistance to inflow is met because of a closed valve at the junction of the two

converging vessels. Forward flow is seen on opening of the valve.

Nicoll and Webb offer several features of both the anatomical arrangement and the behavior of vessels in terminal vascular beds as the regulators of blood flow and blood pressure at this level. *a)* The arcuate pattern of arterioles provides a means for intrinsic regulation of flow and pressure. The roughly concentric organization of the arcuate systems, made up of anastomosing vessels of the same size, serve as volume reservoirs for capillaries. Such an arrangement assures an adequate blood supply for capillary nets which does not fluctuate widely with changes in flow and pressure in single arterial vessels. The authors consider such an arrangement to be necessary in a system in which the demand for blood varies and in which some of the distributing vessels are distensible, thus allowing increases in pressure to be absorbed in the stretched vessels rather than to contribute to increased flow. *b)* The angle of origin formed by an arteriole in reference to its parent vessel affords a means by which pressure may be abruptly reduced. Also, this manner of branching off at a 90-degree angle or more assures an adequate pressure head for each outlet from a given vessel. This arrangement, coupled with the fact that a capillary bed receives blood from several terminal arterioles, results in equal pressure in all capillaries regardless of their distance from their arterial supply. Capillary pressure, sufficient for proper function, can be maintained with minimal arterial pressure. *c)* Nicoll and Webb believe that the Indian Club formation at the arteriolar origins is most important in pressure regulation. The actual size of the orifice of each arteriole aids in reducing pressure from artery to arteriole. The variability in the size of the orifice, which depends on contraction or relaxation of the muscle cells which form it, adds another means of control of pressure in small arteries and arterioles. It is possible that the contraction and relaxation of the muscular elements at arteriolar origins is determined by intra-arterial pressure. This myogenic response would afford another intrinsic mechanism whereby the pressure and flow through capillary nets could be kept at a constant level independent of wide variations among these values in arterial vessels. *d)* Neural control of larger arteries does not seem to be important in the regulation of capillary blood flow. *e)* Active vasomotion in the terminal arterioles causes blood flow through capillary nets to alternate between very vigorous flow and no flow at all. Local conditions determine the degree and

extent of contractile activity of the smooth muscle cells which encircle the terminal arterioles, and therefore local conditions can be responsible for controlling capillary flow to meet the requirements of the tissues in the immediate environment.

Microcirculation in the Rabbit Ear

Collection of new and important data on mammalian small blood vessels began in 1924, following the introduction of the transparent chamber technique by Sandison (104). He reported (106) observations on circulation in the rabbit ear primarily concerned with contractility of small blood vessels. Local control of blood flow was seen to reside in the smooth muscle cells which developed on newly formed capillaries as they were transformed into arterioles. In observing circulation of blood through the vessels which formed in the chamber, Sandison saw an axial stream of cells surrounded by a narrow, clear plasma layer. Leukocytes were thrown into the peripheral layer of plasma and slowly rolled along the vessel wall. An uneven mixture of blood cells and plasma was observed during sluggish or irregular flow through capillary nets, this type of flow resulting from the aphasic and independent contraction of arterioles which causes blood to be fed to the veins through capillaries and venules in a broken stream. "Plasma skimming" was seen mainly in partially contracted vessels or in capillaries connecting two vessels and in which there was no circulation due to equal pressure at each end of the connecting capillary. In a capillary loop, the two ends of which were connected to a larger vessel, plasma flow (indicated by the passage of blood platelets) would continue in the absence of circulation of blood cells. An increase in the blood supply to the larger, parent vessel often caused red blood cells and leukocytes to be forced through the capillary loop. The blood cells were often seen to take long narrow shapes as they were forced through the constricted entrance to the capillary loop.

Although capillary circulation was almost entirely regulated by contraction of the arterial vessels supplying the capillary plexus, flow was seen to be slowed or even stopped by a single leukocyte caught in a constricted portion of a vessel. One of the most favorable places for plugging by a leukocyte was found to be at the origin of the small arterioles from their arteries. This region was normally partly constricted because of the bulging of endothelial cells into the lumen of the vessel. This site bears a close resemblance to the Indian Club structure described by

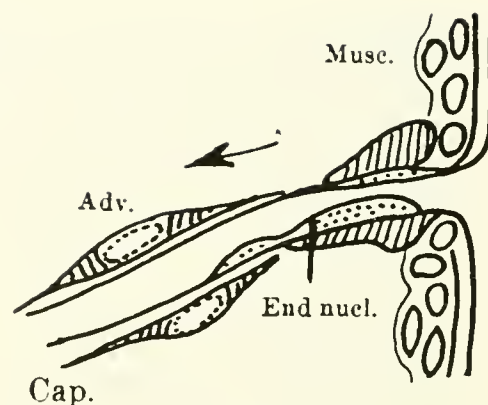


FIG. 4. Camera-lucida drawing of a precapillary branch of an artery. *Musc.* = muscle cells; *End. nucl.* = endothelial nucleus; *Adv.* = adventitial cell; *Cap.* = capillary. [From Sandison (106).]

Nicoll & Webb (89) (see fig. 4). The leukocytes were dislodged by an increase in force of the blood stream or by the ameboid activity of the leukocytes. A similar occurrence was seen by Nicoll & Webb (88) in blood flow through comparable vessels in the bat wing.

Clark & Clark (29), in the same year, reported on the behavior of microscopic vessels seen in the rabbit ear using a "preformed-tissue" chamber, one in which the original structures were present as opposed to newly formed vessels and nerves seen in the first studies using the transparent chamber. The Clarks were impressed with the contraction of arteries and arterioles; spontaneous rhythmical contractions as well as contractions in response to artificial stimulation (mechanical, tactile, or auditory). Spontaneous rhythmical contraction was seen to play an important role in regulation of blood flow, causing changes in the distribution of blood to different capillary areas and causing continuous alterations in the direction of flow. Contractions of arterial vessels were found to be varied. Contraction of the main artery reduced the blood flow to the whole area, but the distribution of blood to different portions was dependent on contractions of different arterial branches, each at a different tempo and independent of the contraction of the main artery and of each other. An arteriole might contract to complete closure and thus cut off blood to the capillaries it supplied while an adjacent vessel, a branch from the same artery, would remain open to allow rapid passage of blood. Arteriovenous anastomoses were seen to contract actively and so influence the distribution of blood. Contractions were seen to decrease in animals that were asleep or anesthetized.

Further studies on the activity of arterial vessels,

including arteriovenous anastomoses, appeared in 1934 (30). Clark and Clark again described the fluctuation in rate and amount of blood flow through any given vessel, as well as the frequent reversals in the direction of flow. A single capillary or venule was seen to have an abundant flow of blood in one direction and a few seconds later an equally great flow in the opposite direction. The variation in flow included scanty flow of a few blood cells, or plasma and platelets only, or stasis, or complete emptying. Such changes were brought about by periodic active contractions of arterial vessels or portions of arterial vessels. The numerous thick-walled arteriovenous anastomoses were most conspicuous for their active contractility. Their contractions were usually more frequent, quicker, and more powerful than those of the arteries, and their effect on venous circulation was more sudden. Definite active contraction of veins was reported to occur near the point of entrance of a cluster of arteriovenous anastomoses.

Clark & Clark (32) studied the growth of capillaries into a transparent chamber and found that new capillaries arose as endothelial outgrowths from vascular endothelium. They advanced as blindly ending sprouts, connecting with neighboring sprouts to form loops, and continued to advance as a plexus with a growing edge of new sprouts. The growing vascular network showed differentiation of vessels in the older portions of the first-formed capillary plexus and many of the capillaries were seen to retract and disappear. An entire chamber was revascularized in 2 or 3 weeks with further differentiation continuing through enlargement of new arterioles which were receiving a large blood supply and widening of venules draining large amounts of blood. There was a further reduction in surplus capillaries. After a few days, the vascular pattern was relatively stable.

The Clarks next directed their attention to the development of extra-endothelial cells on the walls of peripheral blood vessels (33). Three months after vessels had regenerated it was found that venules were wider than capillaries, both vessels having similar walls, while arterioles were as narrow as capillaries and narrower than venules. The walls of the arterioles differed in number and arrangement, and in the form of the extra-endothelial cells. Blood flow was seen to be steady and rapid in arteries and arterioles, steady and slower in veins, and slow with frequent hesitations and reversals in capillaries. Circulation in capillaries was variable, with intervals of steady flow being interspersed with periods of stasis, plasma

skimming, or absence of flow during which the vessels remained open and were filled with plasma. The subsequent fate of the extra-endothelial cells depended on the fate of the vessel on which they appeared. If the vessel remained a capillary, they were occasionally seen to increase in number by mitotic division or to retain the same number. The cells were inert. If the capillaries became parts of venules, the adventitial cells increased in number, retained their longitudinal arrangement, and remained inert. The change of a capillary to an arteriole involved straightening of the vessel, loss of side branches, narrowing of caliber, and an increase in thickness of the endothelium. There was a rapid increase in the number of extra-endothelial cells which assumed a transverse position. Definite active contractility was seen to develop in these cells which became smooth muscle cells, providing they were reached by a regenerating vasomotor nerve.

The caliber changes in minute vessels were discussed by Clark & Clark (34) in 1943. In earlier published studies, the attention of the authors had been on the main arteries, their branches, the arteriovenous anastomoses, and the larger veins. Observations on newly formed arteries indicated that the number of arteries which developed contractility, the rate at which contractility appeared, and its final extent on individual vessels and their branches depended on the rate and extent of growth of new vasomotor nerves. Terminal arterioles in original vascular beds in the preformed type of chamber were seen to show spontaneous contractions which in most cases obliterated the lumen. These vessels could sometimes be made to contract by prodding the animal, but their behavior was erratic. A terminal arteriole was seen to divide immediately beyond its last muscle cell into a capillary plexus. In some instances a terminal arteriole was prolonged for a distance beyond the point of the final muscle cells before forming a capillary plexus. Such vessels had longitudinally arranged adventitial cells rather than muscle cells on their walls. Except for this, they had the characteristics of arterioles, being straight, uniformly narrow, and having a relatively thick endothelium. The region of active contraction was confined to the portion of the vessel which had smooth muscle cells, but the distal portion at times showed a narrowing, with protrusions of endothelial nuclei into the lumen, after blood flow was shut off by active contraction of the proximal portion of the vessel. The vessel showed an increase in caliber following increased blood flow through it. The Clarks refer to these vessels as arterial capillaries.

Microcirculation in the Mesentery

Early descriptions of mesenteric circulation patterns by Zweifach (143) and Chambers & Zweifach (20) dealt primarily with establishing a structural and functional unit, the preferential or thoroughfare channel, which was thought by the authors at that time to be a representative structure of terminal vascular beds. A discussion of the vascular components of the mesenteric circulation and blood flow through them appeared in 1954 (147). Zweifach stated that the mesentery represented a simplified vascular structure devoid of ancillary features peculiar to specific organs. In observing normal circulation in the rat mesoappendix (cecal mesentery), Zweifach found the larger arteries along one side of the mesentery to be about one-third as large in diameter as their paired veins. The depth of anesthesia influenced the caliber of these vessels, deep anesthesia causing them to dilate until both vessels had the same diameter. Respiratory difficulties caused venous constriction. Terminal arterioles in the mesentery proper had a very rapid flow of blood. Collecting veins had a steady flow of blood with continuous forward flow without cessation or temporary reversal. Capillary circulation, however, showed intermittent flow produced by the contraction of precapillary sphincters, the activity of which was irregular and unpredictable. Preferential channels were found to be unusually prominent in the mesentery. The most important structural component for regulating capillary blood flow was the precapillary sphincter. The precapillary sphincter was found at the junction of all offshoots of the muscular components of the vascular bed. The true capillary network was made up of endothelial tubes with no perivascular muscle cells. In some areas the collecting venules were formed by the joining of several side branches leading from precapillary sphincters. Both terminal arterioles and venules were seen to be interconnected to form a series of arcades, so extensive in some cases that they completely circumscribed the capillary bed. The metarterioles originated as offshoots of the arteriolar arcades, extended toward the center of the tissue distributing typical precapillary branches. The arteriolar channels terminated as one or two short capillaries which fed directly into a venous vessel. Zweifach expresses the opinion that the primary mechanisms which readjust circulation through the capillary bed are essentially of a humoral nature. Neurogenic mechanisms, local metabolic factors, and blood-borne substances from organs contribute to the local regulation.

Microcirculation in the Hamster Cheek Pouch

The use of the hamster cheek pouch for microscopic study of the peripheral circulation was introduced by Fulton *et al.* (50, 51).

Although there is no detailed description by these authors of the basic vascular pattern that is seen in this mucous membrane, the literature contains references to the presence or absence of various vascular structures which will be presented here.

The cheek pouch is exceedingly vascular compared to rat mesentery or membranes in transparent chambers. The pattern differs also from the mesentery in that no preferential channels have been found. A rich network of anastomoses between venous vessels and arteriolar vessels is present. Arterioles, which supply the capillary network, bifurcate progressively into branches of equal significance for the distribution of blood (fig. 5). The arterioles exhibit spontaneous vasomotion (80, 82). Lutz & Fulton (81) state that precapillary sphincters were seen to contract independently of adjacent smooth muscle in cheek pouch vessels. Intermittent flow from small veins was also seen, but no venous sphincters were identified.

Lutz & Fulton (81) point out that there is always variation in the demand for blood by the organs, and this variable demand can be satisfied by vasomotor responses without involving the heart or other large structures. The complex anastomosing system of vessels in the cheek pouch, for instance, coupled with vasomotion, permits changes in flow. Neither the vessel wall nor the flow are ever quiescent, the most striking feature of the small vessels being their constant activity.

More vein-to-vein than artery-to-artery anastomoses are seen in the hamster cheek pouch. Venules make up the greatest amount of endothelial surface and contain the greatest proportion of circulating blood at any one time. Lutz and Fulton believe that 60 to 70 per cent of the peripheral circulating blood is in the venous vessels.

Poor & Lutz (97) studied the functional anastomotic vessels in the cheek pouch and reported that artery-to-artery anastomoses were generally one-third to one-half the size of the parent arteriole. These were outnumbered by the vein-to-vein anastomoses. The venous anastomoses were nearly the size of the veins which they connected (fig. 6).

Microcirculation in Skeletal Muscle

The description of the distribution of minute vessels in skeletal muscle has not changed to any marked

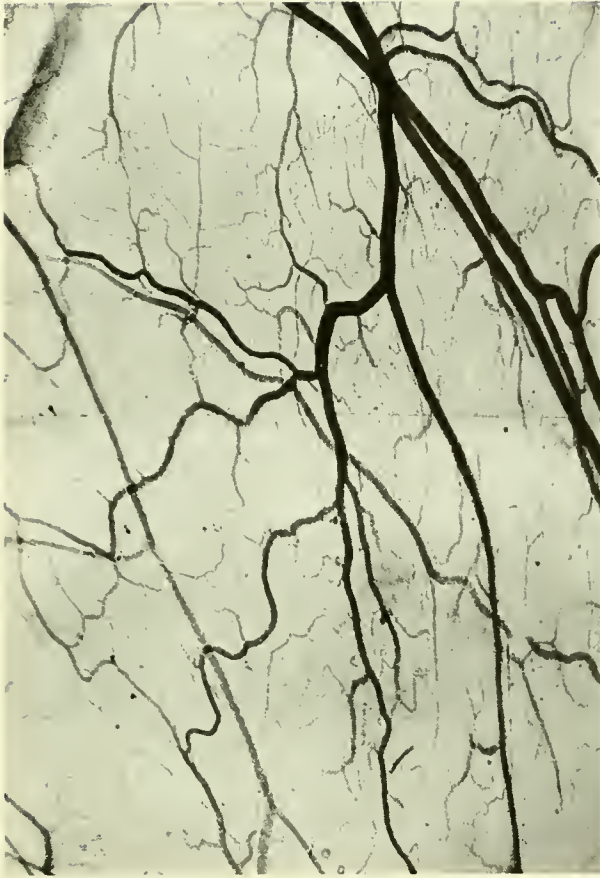


FIG. 5. Vascular pattern of the hamster cheek pouch. (Courtesy of Dr. E. P. Fowler, Jr.)

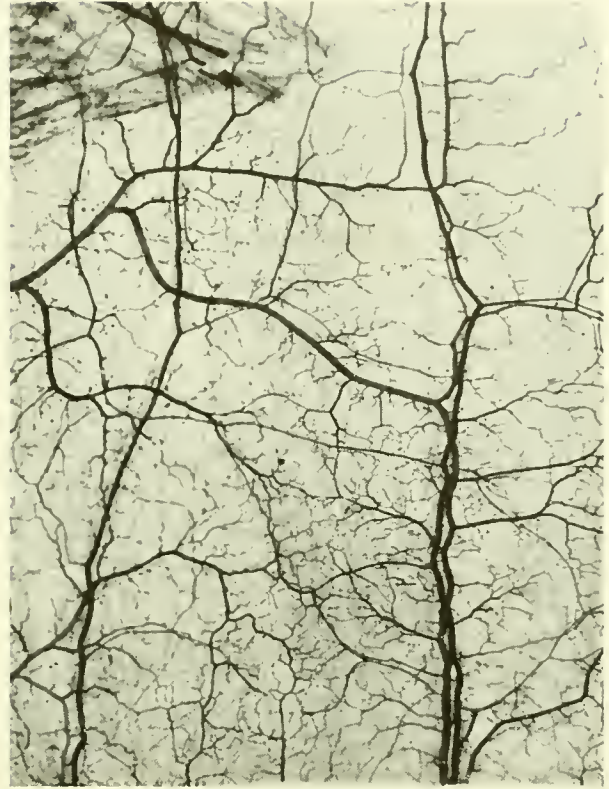


FIG. 6. Vascular network of hamster cheek pouch near buccal end, lead chromate injection. [From Poor (97).]

degree in the last eight decades. The early information comes from studies of injected and fixed material, and in recent years there have been investigations using microscopic techniques on living animals.

Krogh (73) reviews the work of Spalteholz (116), who depicted the vascular arrangement as follows: freely branching arteries with numerous anastomoses between the branches form a primary network which in turn gives off anastomosing small arteries that form a second network. Arterioles branch from this network, usually at right angles to muscle fibers at regular intervals. The arterioles then split up into a large number of capillaries which run along parallel to the muscle fibers with numerous anastomoses. The capillaries unite into venules. The pattern of the venous system is almost exactly that of the arterial systems.

Clark (37) and Walls (126) state that skeletal muscle, which is highly vascular, is supplied by branches from neighboring arteries which invade the epimysium and travel into the perimysium, dividing

as they do so. Various branches of the vessels entering the perimysium anastomose with one another. The finer branches lie transversely to the long axes of the muscle fibers and give rise to the capillaries which run parallel to the muscle fibers. These parallel capillaries lie in the endomysium. This, then, is the anatomical sequence: arteries and veins run together until terminal arterioles and venules are reached. The terminal arterioles and venules then come off of the parent vessels in alternate sequence. The capillaries, running longitudinally between muscle fibers, are connected frequently by transverse vessels which run over or under the intervening fibers and thus form a fine capillary network of tiny oblong meshes.

Zweifach & Metz (151, 152) have studied the vascular supply of the spinotrapezius muscle in the rat. Their observations were primarily of vessels in the epimysium and the perimysium. They found two distinct components in the capillary circulation of muscle bundles, 1) a vascular bed that was distributed along the natural cleavage planes in the connective tissue sheath that binds collections of muscle bundles together, and 2) a second capillary network originated by short muscular arterioles which penetrate into the

depth of the muscle proper and terminate by branching into numerous capillaries.

There are impressive numbers of anastomoses between both arterial and venous vessels which form a series of arcades. Direct anastomoses between arterioles and venules are also found.

The capillary bed of the perimysium is supplied by metarterioles which come off at right angles from the arterial or arteriolar arcades. These metarterioles terminate as one or two capillaries which unite with other capillaries to form venous effluent vessels. The capillaries lie directly on the surface of the small muscle bundles, thus each muscle bundle is surrounded by a network of arterial and venous vessels which interconnect freely with one another within the connective tissue separating the bundles. The muscle fibers are supplied with blood by branches from the arteriolar arcades which penetrate the connective tissue and give rise to capillaries which run along the length of the muscle.

Zweifach and Metz report the presence of metarterioles along the free margins of the skeletal muscle which can be traced directly to the venous system. These vessels, they believe, represent preferential pathways which convey the most rapid stream of blood from the arterial to the venous side.

In addition to structural features, spontaneous vasomotor changes were seen by Zweifach and Metz in arterial and venous vessels. The vasoconstriction was not often intense enough to stop blood flow through the vessels involved, except at the level of the pre-capillary sphincters.

In investigations of red and white skeletal muscle in rabbits (75, 113) injected preparations showed arterial vessels which branched profusely to end in capillaries running parallel to muscle fibers. Also shown were numerous anastomotic connections between small vessels.

Algire (4) and Algire & Merwin (5) studied the panniculus carnosus through a transparent chamber in the rat's back and also saw many arterial anastomoses as well as arteriovenous anastomoses. Arterial branches from the subcutaneous layer supplied the thin striated muscle layer with blood. The arterioles from these branches subdivided into capillaries which ran parallel to the muscle fibers, with cross connections between them, joining other capillaries to form collecting venules.

The capillary blood flow was noted to be intermittent, the result of active vasomotion of the arterioles. Algire & Merwin (5) estimated the length of capillaries that were seen between the muscle fibers

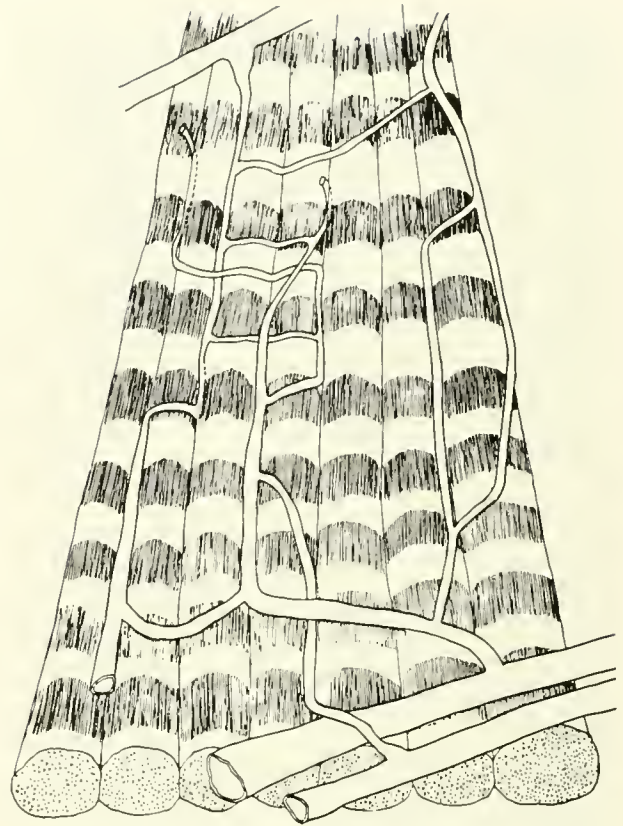


FIG. 7. Capillary vessels in skeletal muscle.

to be between 0.3 and 1.0 mm, with anastomoses occurring at intervals of about 0.1 mm.

Observations of the capillary network of the skeletal muscle bands that course through the bat wing show a vascular pattern similar to the descriptions given above (see fig. 7).

There are notable differences between the distribution of capillaries in the endomysium and that in the areas adjacent to the skeletal muscle. The vessels which run parallel to the muscle fibers are generally longer and straighter than comparable vessels in the surrounding connective tissue. An arteriolar branch that crosses the muscle fibers often subdivides into two capillaries that originate at right angles to the parent vessel and go off in opposite directions. They usually do not lie in the same plane, one going deep between the fibers, occasionally until lost from view, while the other vessel continues on the upper surface. As a result of this downward, or sometimes upward, turn it is possible to look directly down into the lumen of a capillary rather than at the customary longitudinal view. An arteriole with its accompanying venule may cross the muscle band without either of the vessels

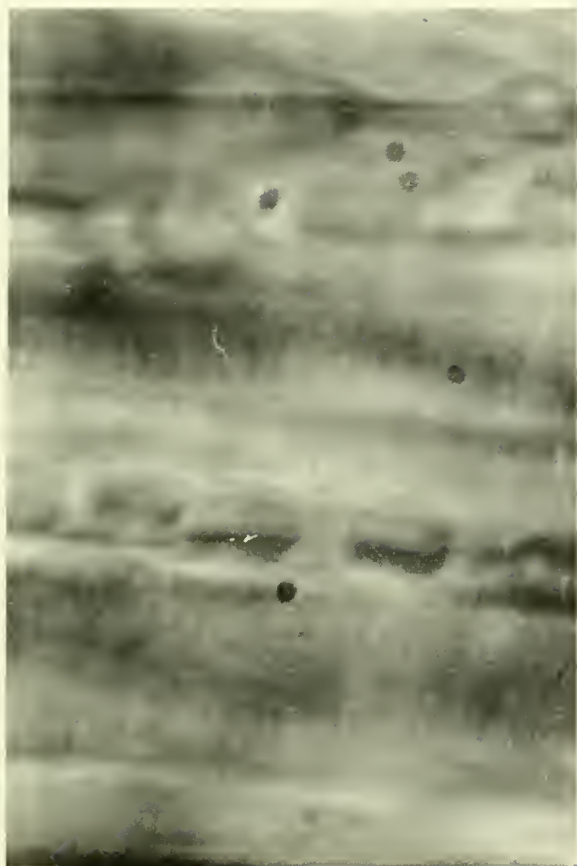


FIG. 8. Red blood cells "on edge" in a capillary of skeletal muscle.

giving off branches to contribute or to receive blood from the underlying muscle. When capillary vessels running parallel to the muscle fibers are confined to the narrow space between two fibers, the capillaries are flattened and the cells face the fibers (fig. 8), as reported by Reynolds *et al.* (100) in similar vessels in the myocardium. In a wider space, the cells are often seen broadside.

Anastomoses between the capillary vessels running parallel to the muscle fibers are numerous, the connections occurring sometimes between adjacent vessels and just as frequently with vessels lying some distance away. Short connections between arterial and venous pathways are also seen.

Intermittent flow occurs in the capillaries of these skeletal muscle bands as a result of spontaneous closure of short duration of terminal arterioles that give rise to the capillaries which lie in the endomysium.

Studies made thus far in these beds have established no characteristic pattern formed by vessels supplying the muscle bands that deviates from what is normally

seen elsewhere, except for the parallel course of the vessels lying between the muscle fibers.

Microcirculation in Myocardium

There is a paucity of descriptive literature on the capillary beds in the myocardium. Although a few investigations on fixed material appear, no studies have been made on circulation through the minute vessels in the living animal, presumably because of the difficulty of microscopic observations of an organ in motion.

In 1928, Wearn (127) studied sections of myocardium obtained from man, cats, and rabbits. The vessels were filled with material injected through coronary arteries. Wearn observed that almost every cardiac muscle fiber was in direct contact with one capillary and some fibers were touched by two or more. A muscle fiber was completely surrounded in some instances due to numerous anastomoses between capillaries. These interconnecting branches ran across the parallel muscle fibers. Capillary vessels were found to lie between the cardiac muscle fibers and did not actually penetrate the muscle substance.

Saunders & Knisely (107) reported having watched through a microscope the circulation in the myocardium of beating frog hearts. Blood flow was seen to stop during systole and to flow profusely during diastole. The cessation of flow in systole was brought about by compression of the small vessels by the contracted myocardial fibers.

Reynolds *et al.* (100) studied fixed sections of heart muscle, the hearts having been taken from dogs without loss of blood from the coronary vessels. They report that capillaries had a diameter of approximately $4\ \mu$. The capillaries were seen to run along the muscle fibers as described by Wearn (127), about one capillary to every muscle cell. The orientation of the red blood cells within the capillary vessels was believed to be unusual, in that the cells were often seen edgewise, i.e., with the flat surface of the red cell facing the parallel myocardial fibers. The authors conclude that the capillary vessels running between the muscle fibers are elliptical in cross section rather than round.

In normal hearts, more capillaries were found in the epicardium than in the middle portion or the endocardium. Various explanations, none conclusive, were given for this.

Terminal arterioles were identified by the presence of an endothelium with distinguishable smooth muscle cells along their walls. The terminal arteriole gave rise

to a number of capillaries that ran parallel to each other in the same direction as their parent vessel.

A postcapillary venule was formed by the union of capillaries which came from opposite directions along the muscle fibers. The postcapillary venule increased in size as it was joined by similar tributaries. These tributaries formed venules, which were identified by their muscular walls.

Provenza & Scherlis (99) studied sections made from dog hearts and placed great emphasis on the appearance of "muscle sphincters" in various small vessels. Although the authors have used the terminology of Chambers & Zweifach (20), it has not in every instance been properly applied, and comparison with other terminal vascular beds is difficult. A highly imaginative diagram indicates the presence of arteriovenous anastomoses, metarterioles, thoroughfare channels, and precapillaries.

Microcirculation in Skin

Zweifach (149) has presented a description of the cutaneous circulation in a flap of skin of the rat from which the connective tissue had been cleaned off.

A network of arterial vessels in the connective tissue between the skin and underlying muscle gives rise to small arteries which enter the dermis. These small arteries, as well as the ones from which they originate, form a regular pattern of interconnecting links or arcades. The capillary bed of the dermis is composed of a secondary network lying between the interarcading arterioles. This secondary network is formed by precapillary and capillary vessels that are branches of the interarcading arterioles.

Blood flows away from the capillary bed in wide vessels, which join to form collecting venules. The collecting venules form an interconnecting plexus that is similar to, but more extensive than, the arterial plexus. Many short arteriolar branches are seen to go directly into the vessels of the venous plexus. Also seen are direct connections between arterial and venous arcades that allow blood to go from arterial to venous side without going through a capillary network. The venous vessels form the major portion of the cutaneous vascular beds.

Zweifach believes that the branches which leave the arterial arcades are structurally similar to metarterioles in that they have a thin layer of smooth muscle and a comparatively straight course. The vessel finally becomes part of the capillary bed after giving off branches along its course. These offshoots, or side branches, are precapillary vessels, having

spirally arranged muscle cells in the immediate junctional region. The precapillary vessels show characteristic spontaneous vasomotion. Vasomotion is also seen in the deeper lying arterioles. The small venules of the cutaneous bed show a continuous almost rhythmic pattern of spontaneous activity that is unrelated to the vasomotion of the deeper lying vessels.

The arteriolar arcades were found to be very responsive to constrictor and dilator agents. The venous arcades showed a 20-fold increase in responsiveness to epinephrine when the temperature was made to fall 1 or 2 degrees, indicating that they are greatly influenced by temperature change. Zweifach considers the venous network in the skin to be unique in this regard.

From his studies, Zweifach concluded that the structural pattern of the cutaneous circulation was atypical, since it was composed predominantly of highly reactive venous vessels. The circulation in the skin appeared to be regulated locally by tissue mediators.

The description of the cutaneous vascular pattern and its vasomotion conforms in most respects to that of other terminal vascular beds that have been studied, with the possible exception of the mesentery and the omentum. The interconnecting arcades of both arterial and venous vessels with a secondary network forming the capillary bed are prominent features of the pattern of small blood vessels in the hamster cheek pouch and the bat wing. Such an arrangement seems to be a common denominator in vascular patterns of the microcirculation.

Microcirculation in Stomach and Intestine

Until a recent paper by Baez (6), descriptions dealing with the vascular patterns of small blood vessels in the stomach and intestine have been based on injected and fixed material. It is extremely difficult to establish the paths of blood flow in a tissue without observing the flow in living material. This would apply especially in such a vast network of venules and arterioles which intercommunicate so freely by a system of arcades as is present in the musculature of the gut. Although the early investigations briefly discussed here are not concerned with the smallest vessels, they will serve as a background for a more detailed description of the terminal vascular beds of the alimentary canal.

Noer (90) studied the vascular patterns in the jejunum and ileum of specimens prepared by liquid latex injections. The descriptions are of the mesenteric circulation and the superficial vessels of the gut wall

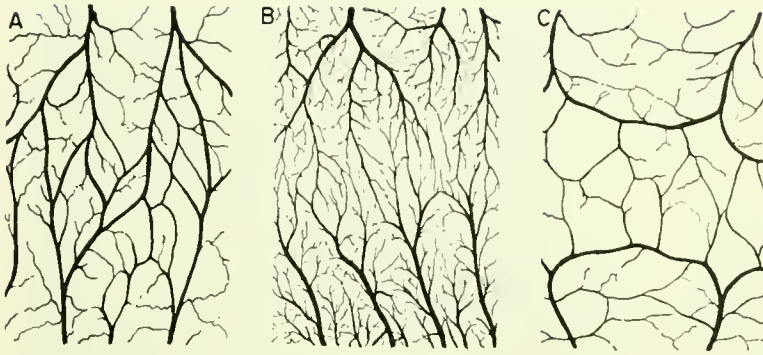


FIG. 9. Types of antimesenteric area anastomoses. [From Noer (90).]

(the mural trunks). In his search for an experimental animal which might have a vascular distribution similar to man, he observed 14 different animals. The basic architecture was found to be similar in all animals in that the intestinal arteries formed mesenteric arcades or arches which in turn gave rise to vasa recta, which then proceeded to the intestinal wall to form mural trunks. Striking variations in the numbers of mesenteric arcades were found among the species as well as differences in the pattern of the vasa recta, including their length and whether or not they had anastomotic connections with one another. The mural trunks in the human stomach were found to ramify in two ways, a similar arrangement being seen in other animals. A single vessel passing to the antimesenteric area might give off lateral branches along the way, or the vessel might break up into several branches rather quickly and subdivide in an arborescent fashion. Three types of anastomoses between the mural trunks in the antimesenteric area were found to be 1) direct communication between the mural trunks of the two sides, 2) a plexiform arrangement, 3) short vessels joining arcuate mural anastomoses (fig. 9). Veins were found to follow the arteries with few exceptions.

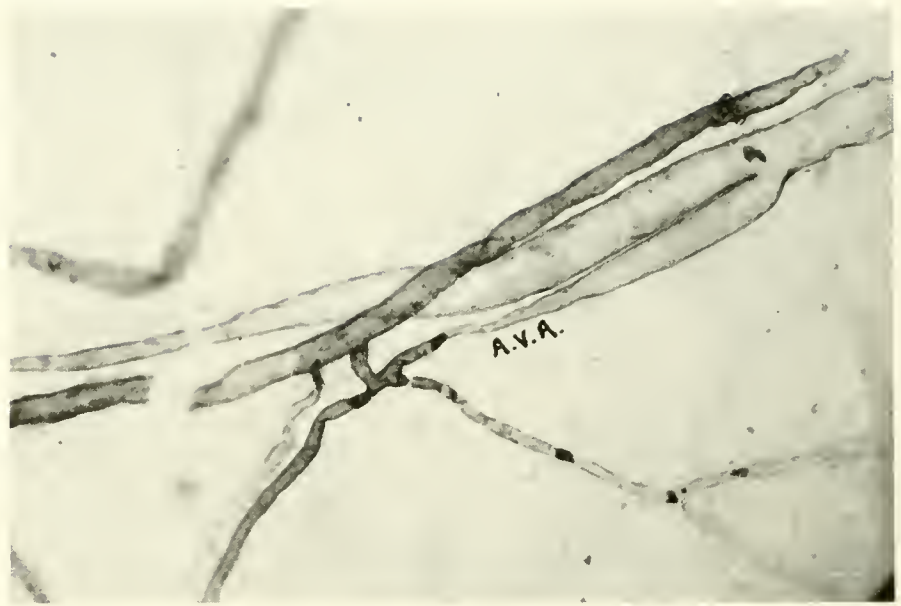
Although Noer was not the first to describe the arcuate patterns found in the arterial and venous vessels of the intestine, his report is extensive and detailed, and contains a comprehensive review of the literature up to that time.

Investigations of the alimentary tract during the next few years centered around the absence or presence of arteriovenous anastomoses, especially in the human stomach. Barclay & Bentley (7), stimulated by the findings of Trueta *et al.* (120) of vascular shunts in the kidney, proposed that in the wall of the stomach there were arteriovenous anastomoses in the region of the submucous plexus, and that when these arteriovenous anastomoses were open, active circulation through the vessels of the mucous membrane was

excluded. Their conclusions were based on the absence of radiopaque material in the mucous membrane of stomach injected immediately after surgical removal. They suggest that the injected material flowed from arteries of the submucosal plexus to the gastric veins directly through a shunt located in the submucous plexus. In 1952, Walder (125), accepting the presence of arteriovenous anastomoses in the submucous layer of the human stomach after what seemed to be confirmation of them by Barlow (8) through microdissection, carried out investigations to determine their function, size, and responses to stimuli, both physical and pharmacological. Cannulation of the right gastroepiploic artery and its accompanying vein permitted him to introduce glass beads, 40 to 200 μ in diameter, into the artery and to recover them in the venous outflow. The presence of spheres, 140 μ in diameter, in the venous outflow was believed to be indicative of patent arteriovenous anastomoses, because spheres of this size could not travel through the capillary network. The results of the injection of drugs, nerve stimulation, and varying perfusion pressures to determine their influence on the size of the arteriovenous anastomoses were inconclusive.

In an extensive study of the vascular patterns in the alimentary canal, Barlow (8), in describing the arterial supply to various portions of the stomach, notes frequent anastomoses of the arteries in the submucous plexus and the mucosa. The mucosal arteries give rise to capillaries which also have anastomotic connections. He found arteriovenous anastomoses in the stomach which consisted of an arterial end, variable in length, a short narrow junction area, and a short wide venous channel. This structure was demonstrated by Barlow's double injection technique. The arterial end may be a direct branch of a mucosal artery or arise from a main channel in the submucous plexus. It terminates by joining either a distant mucosal vein or may double back on itself and anasto-

FIG. 10. Arteriovenous anastomosis in the submucous plexus.
[From Barlow (8).]



mose with a tributary of its accompanying vein (fig. 10).

In 1959, Baez (6), using the small intestine of the rat, gave a detailed account of the vasculature at various levels based on observations in the living animal. In discussing the method of observations, Baez points out the advantage of having an intact animal in which the distribution of large supplying arteries and accompanying veins of the wall as well as their relation to the small vasa recta can be determined. The type of a vascular connection at the antimesenteric border as well as the vessels of the submucosal plexus and the final ramifications of the vessels to the muscular coat can be established.

The description of the vessels in the submucosal plexus is as follows: Main arteries ($60\text{--}80\ \mu$), which pierce the muscularis in the mesenteric region at intervals, divide into two or three branches in the submucosa. Each branch subdivides into four or six smaller branches ($30\text{--}40\ \mu$) which then proceed to the antimesenteric border where they connect with similar arterial branches from the other side. Other arterial anastomoses are formed by interconnections of branches between neighboring recta. Baez uses a general description for main arterial arcades with three characteristics: 1) they are located in the outer plane of the submucosa and average 30 to $40\ \mu$ in diameter; 2) all give rise to secondary arcades, mucosal arteries, and vessels to nourish the muscular coat; 3) the direction of blood flow through them is changing constantly.

The small vasa recta which arise from the last

mesenteric arcade terminate quickly by anastomosing with secondary branches of other arcades. The small vasa recta lie between the large vasa recta. They supply the vessels to the submucosa and muscular coats of the gut wall near the mesenteric border (fig. 11). These vessels go in opposite directions, some to the outer smooth muscle coat and others to the inner absorptive surface of the gastrointestinal tract. They seem to have a unique type of blood flow. Unidirectional flow in the large and small vasa recta is altered in the meshwork of interconnected arterial vessels in the submucosal plexus. A main arterial arcade may show complete reversal of flow or, as more frequently happens, blood may flow from both sides of an arterial arcade into a mucosal artery. At times, when blood is rushing into an arcade from opposite directions, the converging currents may produce a space of clear plasma at the point where they meet. When this occurs at the origin of a mucosal vessel, plasma is "skimmed" into it.

The muscular coat of the ileum is supplied by vessels that originate from the proximal end of mucosal arteries or from secondary arcades in the submucosa. Baez considers these vessels to be metarterioles, 18 to $24\ \mu$ in diameter, which enter the muscularis and run in the plane of cleavage between the circular and longitudinal muscle bundles. In the intermuscular septum the capillaries for the circular muscle bundles stay on the same plane as the parent vessel, while those for the longitudinal muscle bundles turn outward. The capillaries communicate freely to form a network, both in the same plane and

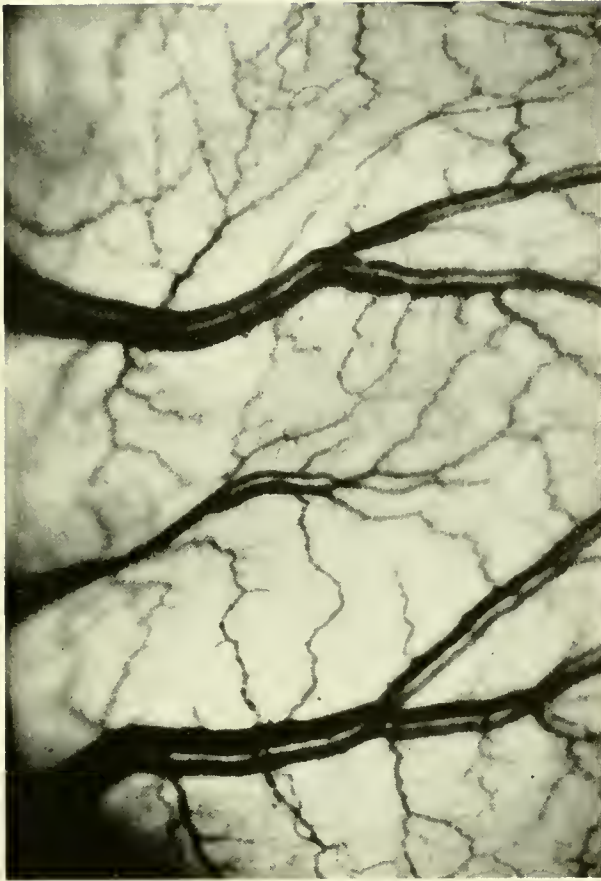


FIG. 11. Photomicrograph from the anterior wall of rat ileum. (Courtesy of Dr. Silvio Baez.)

between adjacent layers of muscle. The parent vessel either divides in two, or arches and becomes a venule which is joined by venules from neighboring capillary nets before entering a submucosal vein. Such an arrangement, whereby a metarteriole leaves the submucosa and enters the smooth muscle coat where it gives off a capillary network and then returns to the submucosa as a venule, constitutes, according to Baez, a distinctly organized terminal vascular unit.

The minute vessels of this unit are both muscular and nonmuscular, the muscular component being the centrally located metarteriole and the precapillary vessels which branch from it and in turn give rise to the nonmuscular capillary network. The muscular vessels and their parent metarterioles are considered by Baez to be the most highly reactive of the mural vasculature, a fact demonstrated by vasoactive drugs and varying intraluminal pressures. The capillary bed of the muscular coat of the gut, which is served by these metarterioles, shows periodic changes in blood flow; the changes being independent of flow

through the arterial plexus of the submucosa. The muscular coat may be devoid of circulation while blood continues to flow through arteries of the submucosa and mucosa.

In some instances the parent vessel may begin as a short arteriole, rather than a metarteriole, which in turn then gives rise to several metarterioles when it reaches the muscular coat. The pattern of distribution is then the same as described above; the metarteriole forms a central channel, and turns inward to become a venule or breaks up into two or three capillaries.

The mucosal artery continues toward the muscularis mucosa after having given off the vessels just described which go to the outer muscular coat. One or two short vessels are now seen to branch from the mucosal artery. The short vessels subdivide into several capillaries which reunite as a venule and empty into a submucous vein. Deeper in the submucosa all mucosal arteries anastomose with a similar mucosal artery and give rise to one or two branches which in turn subdivide to form capillary nets. The mucosal artery terminates by penetrating the base of a villus.

Baez was unable to find any arteriovenous anastomoses in the submucosa of the jejunum or ileum. It was possible to follow all the arteries and arterioles of the submucous plexus to their finest ramifications without observing any short cuts from the arterial to the venous side. This was also true in vessels in the muscular coat. He does elaborate, however, on the direct connection between arterioles and venules at the bases of villi. While the arterial component does deliver arterial blood directly to the venule which drains the villus, it cannot be called a true arteriovenous anastomosis in that the arteriole gives off branches to neighboring structures. The location of these vessels is the same as the location of vessels described by an earlier investigator (117) as arteriovenous anastomoses. Baez points out that in an injected and fixed preparation the capillary offshoots might be closed, giving the appearance of a true arteriovenous anastomosis.

Two or three venules from adjacent villi were seen to converge to form a mucosal venule. The mucosal venule also was joined by an arterial capillary which originated as a branch of the nearest mucosal artery. The small vein thus formed then emerged into the submucosa where it was joined by other veins of similar origin to form an intricate anastomosing arcade. These submucous arcades were further enlarged by venules from the outer muscular coat. The flow of blood through the venules of the muscular

coat and the mucosal venules was rapid and unidirectional. Backflow of blood was observed in veins of the submucosal plexus.

Microcirculation in the Bulbar Conjunctiva

The bulbar conjunctiva is a highly vascularized transparent mucous membrane on the anterior surface of the eye. It extends from the palpebral conjunctiva, which lines the eyelid, to the cornea. The pattern of its blood vessels were derived primarily from studies by Grafflin & Corddry (56) and Lee & Holze (77).

A description of the arrangement of the superficial blood vessels of the human conjunctiva is given by Lack *et al.* (74) in a study designed to observe vascular changes in hypertension. Arterioles were seen to divide into numerous side capillaries and terminate with an end capillary. The term "end capillary" is not defined. The end capillary on occasion functioned as a "through-and-through" channel. The capillaries appeared to be uniform in caliber. Only rare arteriovenous anastomoses of the short type were seen.

A more detailed description appears in a paper by Lee & Holze (77) in 1950, in which they state that the arrangement of terminal arterioles, capillaries, and venules in the human conjunctiva was in accord with the pattern of vessels as seen in the omentum and mesentery of other animals, referring to the descriptions of Chambers & Zweifach (20) and Lee & Lee (78). Capillaries arose at intervals from end arterioles to form an irregular network of vessels which then rejoined to form the venular system. The arterioles were also seen to terminate in main channels which communicated directly with a venule. This pattern was most often seen at the corneoscleral junction. It was also noticed that blood continued to flow from arterioles to venules, through the patent arteriovenous channels, at a time when there was widespread arteriolar and precapillary constriction. The precapillaries were found to be more sensitive to stimuli than their parent arterioles.

Observations of blood flow revealed active contraction of vessels. Constriction of precapillaries was seen to occur at their point of origin from the parent arteriole. Attention was directed to these precapillary sites because of the difficulty in determining minor changes in diameter or flow in the arterioles. Complete constriction occurred at the precapillary region lasting for 2 to 3 min. After a gradual relaxation, blood flow continued for 1 to 5 min before the next constriction. The periods of constriction and relaxa-

tion were found to be very irregular, with relaxation predominating.

Arteriolar flow was rapid, capillary flow was slower, and also intermittent due to spontaneous changes in diameter at the precapillary sites, while venous flow speeded up after entering the system of collecting venules and was consistently regular.

The proposal of a definite structural and functional unit, such as the preferential channel, as described by Chambers & Zweifach (20) in the rat mesentery and seconded by Lee & Holze (77) in the human conjunctiva, prompted Grafflin & Bagley (55) to reinvestigate the human conjunctiva. These investigators were impressed by an endless variety of vascular patterns with no apparent plan of organization. This paper was followed by one by Grafflin & Corddry (56) who reinvestigated, with improved equipment, the architecture of vascular beds in the human conjunctiva in an effort to resolve the differences between the earlier observations and those of Lee & Holze (77). Once again they reported a great variety of vascular patterns with the lack of any recognizable structural and functional unit similar to that proposed by Chambers & Zweifach (20). They saw, however, vessels between arterial and venous channels that were larger than capillaries. They believed that these vessels were arteriovenous communications with a functional significance different from that of capillaries. They do not say what the difference is. The arteriovenous communications were seen so frequently that the investigators believed that they were a characteristic feature of the conjunctival vascular beds. In freehand drawings at magnifications up to 80 times, a variety of vascular patterns are shown. The arteriovenous communications, veno-venous anastomoses and arterio-arterial anastomoses are common features (fig. 12). Although at first glance the vascular pattern may seem very complex, it is comparable in its arrangement to other terminal vascular beds which have been presented in such detail covering a large area. A smaller area is seen in figure 13.

A representative type of arteriovenous anastomosis, as seen in vascular beds below the surface of the conjunctiva (presumably on the episcleral surface), is shown in figure 14. It bears a striking resemblance to both photomicrographs and diagrams of the vascular bed in the rat mesoappendix. The authors do not describe the kind of blood flow through these vessels which would qualify them as preferential channels on a functional basis.

The vascular patterns presented by these authors



FIG. 12. Superficial vascular pattern, temporal quadrant, right eye. [From Grafflin & Corddry (56).]

may be considered to contain all the blood vessels in the areas under observation. While the walls of capillaries were never seen and their detection is dependent on the presence of blood in the vessels, it is unlikely that the same vessels would be devoid of blood consistently over a period of months during which repeated observations were made.

Vasomotion was a prominent feature of flow in the vessels of this mucous membrane. It was indicated by variations in the speed of flow, alterations in the caliber of individual vessels, and intermittent blood flow through capillary vessels. Arterial vessels usually



FIG. 13. Superficial vascular pattern, nasal quadrant, right eye. [From Grafflin & Corddry (56).]

had a rapid and continuous flow. At times the arterial vessels showed irregular alterations in the rate of flow, a reduction in the speed occurring sometimes gradually, sometimes abruptly, and sometimes stopping completely for a brief interval before surging forward.

Concerning small arteriovenous communications, there are three criteria to distinguish them from true capillaries: 1) a larger caliber than capillaries, 2) vasomotion, 3) continuous flow at variable speeds. However, one or all of these criteria might be unsatisfied on occasion. Grafflin & Corddry (56) were unable to detect precapillary sphincters at the points of emergence of true capillaries from the arteriovenous channels. It may be assumed that this failure was due to the limitations of the technique, in that the walls of the small vessels were not seen distinctly.

Venous flow is described as being continuous at a relatively moderate speed with irregular alterations in flow. At times the flow stopped completely. This does not concur with the description given by Lee & Holze (77), who reported venous flow as consistently regular.

Bloch (15), in a lengthy article dealing primarily with red cell aggregates, describes arterioles and venules in the bulbar conjunctiva in the following way: Arterioles in the bulbar conjunctiva do not differ from arterioles in other tissues. As elsewhere,

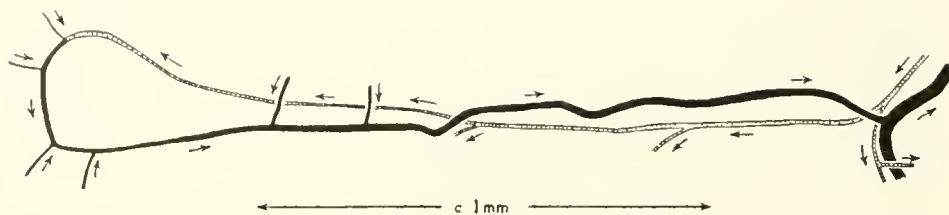


FIG. 14. Prominent arteriovenous anastomosis lying below the superficial layer of the conjunctiva.
[From Grafflin & Corddry (56).]

arterioles are most readily identified by noting the direction of blood flow. The direction of flow in these vessels is toward progressively smaller vessels, and the smallest of them empty into the capillary bed. Bloch states that when there is a low blood volume, only one capillary may be seen connecting the arterial and venous systems. The arterial segment of this single vessel has a more rapid rate of flow through it (does not say more rapid than what), differs in regard to the direction of taper of its walls (presumably larger at the venous than the arterial end), and is less permeable than the venous segment (no basis given for this statement).

Bloch feels that the difficulty in determining which vessel is an arteriole has arisen partly because of sudden changes in the direction of flow. According to Bloch, changes in direction occur when an arteriovenous anastomosis opens, causing flow in the peripheral segment of the arteriole to stop while flow in the central portion of the venule speeds up. He states that there is no difficulty in recognizing the cause of this directional change if the arteriovenous anastomosis opens while the observer is watching and when the site of the arteriovenous anastomosis can be found. He further states that usually the site of the arteriovenous anastomosis is not identified.

Linear velocity of arterioles is greater than venules of corresponding diameter. The course of the arterioles is straight compared to the relatively sinuous course of the accompanying venules. Arteriolar branches arise gradually from their parent vessels, while venules branch more nearly at right angles. Arterioles are deeper in the tissue than corresponding venules, their flow rates being so rapid that individual cells cannot be recognized.

Capillaries are described as cylinders, in contradistinction to arterioles and venules which are cones.

Some difficulty arises in comparing the descriptions of the vascular structure as given by Bloch with that of other investigators due to the absence of detailed diagrams. True arteriolar branches are not represented in other vascular beds as branching

gradually, although this type of branching occurs in vascular nets forming arcuate systems.

Microcirculation in the Spleen

Differences of opinion regarding the manner in which blood is conveyed from terminal arterioles to collecting venules in the spleen still exist in spite of the continued efforts of numerous investigators to resolve the controversy. Current histology textbooks (9, 112) present three views. The theory of closed circulation is that blood in the spleen flows through completely endothelium-lined pathways from its entrance into the spleen through the splenic artery to its exit from the spleen through the splenic vein. The theory of open circulation proposes that arterial terminations in the spleen pour blood flowing through them into the interstices of the reticulum of the red pulp. The walls of the venous sinusoids are incomplete, having longitudinal slits between the reticular cells which make up the lining of the sinuses. A third view is a compromise between the open and closed systems in that some of the capillaries are thought to open into the intercellular spaces while others open directly into the sinuses.

It was hoped that the introduction of a technique which permitted observation of the spleen of a living animal might settle the controversy. In 1936, Knisely (69) studied living transilluminated spleens of mice, rats, and cats and reported that each vessel traced in the spleen was connected to the arterial system and the venous system. No vessels were seen to open out into or pour blood into intercellular pulp spaces. The lining of the arterioles, arterial capillaries, capillaries, venous sinuses, and venules was readily apparent through the microscope as a narrow, clear, sharply refractile line, visible also during periods when no blood was flowing through the vessels. Knisely's conclusion was that the vascular system of the spleen consisted of a series of completely interconnected, preformed, lined channels. He describes spontaneous vasoconstriction in the arterial branches

as well as in the venous sinuses, and assigned this normal activity of vascular smooth muscle to "physiological sphincters." No significant differences were noted in the structure or activities of living mouse, rat, and cat spleens.

In 1941, MacKenzie *et al.* (83) reported that they had been unable to confirm Knisely's findings. They point out that the modern consensus favored a splenic circulation that had an open component which allowed flooding of the pulp interstices with whole blood, and additional pathways afforded a closed circulatory component. The reception of Knisely's investigations had been favorable and "offered a reasonable conclusion to an otherwise apparently interminable discussion." However, they were not able to see what Knisely had seen. In transilluminated spleens of mice, the walls of follicle arteries were seen as sharply refractile lines, running parallel, the diameters of the vessels uniform except when constriction occurred. The follicle arteries branched two or three times to form penicilli, synonyms being pulp arteries, sheathed arteries, or pulp arterioles. They were able to see only the peripheral portion of the follicle capillary network, the ultimate twigs penetrating the marginal zone of the red pulp. Terminal capillary branches, as many as eight in number, enter the adjacent red pulp and develop funnel-shaped dilatations. These arteriocapillary ampullae communicate directly with the pulp interstices by way of numerous apertures. As the lumen of the capillary widens in the formation of its ampulla, the refractive quality of the vessel wall is rapidly lost. The parallel linear shadows produced by the capillary are replaced by the contours of pulp cells.

Venous sinuses originate in the red pulp by an enclosure of pulp spaces. A venous sinus gradually increases in diameter to a maximum and then joins a vein. The wall of the venous sinus is composed of loosely connected cells lying parallel to the long axis. The openings between these cells, according to MacKenzie *et al.*, permit the free passage of blood cells.

The interstices of the pulp provide the one and only type of connection seen by them to link the arterial and venous systems in the spleens of mice, rats, rabbits, guinea pigs, and cats. They state, however, that in all spleens there were instances when an arterial capillary appeared to be connected by a vessel to an adjacent venous sinus, but this proved to be an optical illusion caused by weaknesses inherent in the transillumination technique. Spontaneous

arterial vasoconstrictions were seen to occur intermittently and were a factor in the control of circulation of blood through the small vessels as were trabecular and capsular contractions. MacKenzie *et al.* believed that the results of their work supplied additional confirmation of an open circulation for the mammalian spleen.

Bjorkman (11) studied rabbit spleens following the injection of starch granules and concluded from the distribution of the grains that circulation through the spleen was the open type.

A detailed and convincing report in favor of the closed system of circulation appeared in 1951, authored by Peck & Hoerr (94). They selectively attacked statements made in the paper by MacKenzie *et al.* (83), pointing out where possible technical variances could explain the differences in their observations. Peck and Hoerr found the intermediate circulation of the spleen of the mouse to be essentially as Knisely (69) described it. They say that, on arriving at the red pulp, arteries branch two to six times to form the penicillar arteries which then extend into the red pulp 10 to 15 μ before branching several times to form capillaries. Where more than two capillaries arise from a red pulp artery, the termination of the artery may be ampulla-shaped (see fig. 15). There is no discontinuity of the refractile lines from artery to capillary, and these lines caused by the vessel walls must be endothelium or reticular fibers. Capillaries extend in all directions from the ampulla-like terminations of the penicillar arteries to terminate in venous sinuses or venules (fig. 16).

The course taken by a capillary may be straight, curved, or tortuous. If they have a tortuous course it is often difficult to follow them because they run under other vessels or extend beyond the range of focus. Capillaries may turn away from view at their point of origin, giving the ampulla-like termination of the penicillar artery the appearance of ending in a sac or pouring its blood into the pulp. The capillaries can be seen to terminate in the venous sinuses, the walls of which (more difficult to see in the contracted spleen) are continuous with the walls of the capillary.

Penicillar arteries have a powerful sphincter action, although an artery may contract along its entire length. Individual arteries may exhibit this constriction independently of neighboring arteries, which continue to have a rapid flow. Fairly constant blood flow over a period of hours is seen in straight capillaries which terminate in venules. In some cases red cells may seem to wander in the extravascular tissue,

FIG. 15. An ampulla of a red pulp artery.
[From Peck & Hoerr (94).]

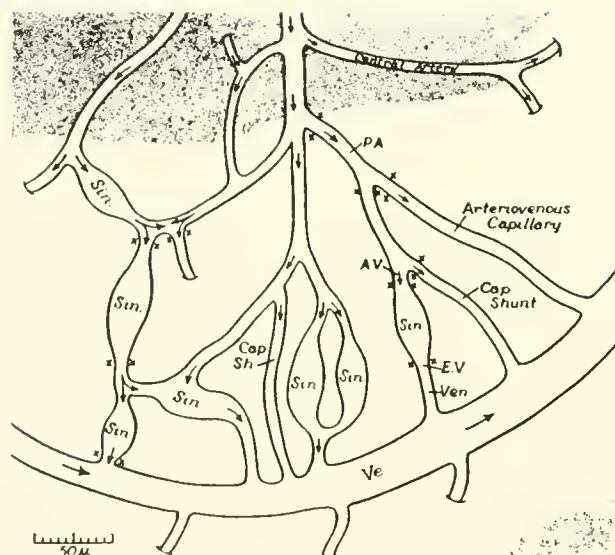
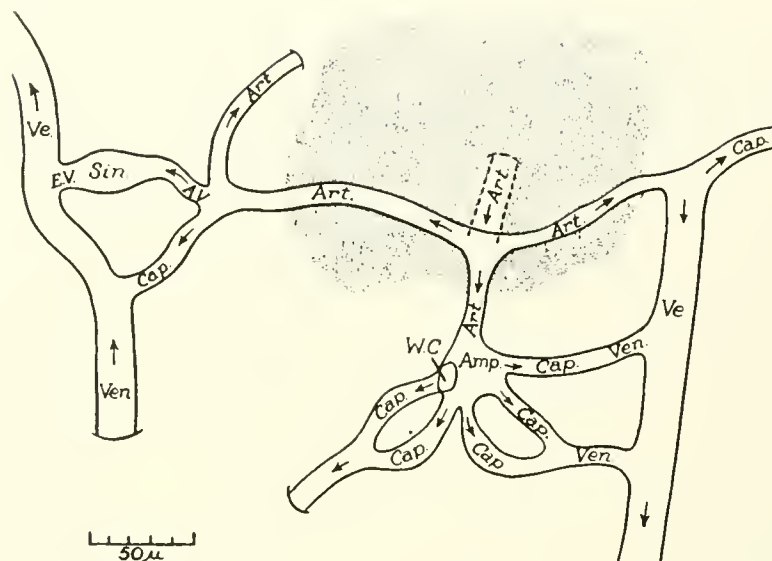


FIG. 16. Diagram summarizing the main types of arterio-venous connections in the mouse spleen. [From Peck & Hoerr (94).]

but proper focusing shows them to be within tortuous capillaries.

Peck and Hoerr conclude from their observations that blood in the spleen passes through lined, intact blood vessels which join the arterial and venous systems.

The next major reports on intermediate circulation in the spleen were by Parpart *et al.* (93) and Whipple *et al.* (133), and favored open circulation. These investigators saw three ways in which trabecular arteries, terminating as arterioles, connected with

collecting veins. Most of the arterioles spewed blood through funnel-shaped openings into large pulp spaces from which the blood flowed into collecting veins. Some of the arterioles made direct connection with collecting veins, and such connections were called arteriolar-venous anastomoses. A few of the arterioles were seen to branch into a loose, irregular capillary network which formed venules that returned to the collecting veins. Considering each component of the system from arteriole to veins separately, Parpart *et al.* (93) state the following: Terminal arterioles are thick and muscular and show continuous diameter changes due to constriction and relaxation of the vascular muscle. The terminations of these arterioles are usually three-dimensional and funnel-shaped with the flared ends becoming too thin to be seen with the microscope. This indicates, according to Parpart *et al.*, that the flare thins out to a condition of no endothelial covering of the blood that flows out of the ampulla into the pulp. The pulp space may be fed by only one arteriole or by several. Pulp (reticular) cells are scattered throughout the space seemingly held in position by connective tissue strands. Red and white blood cells can be seen to enter and leave the main stream of blood flowing through the pulp space, remaining outside the stream and thus stationary for variable periods. The pulp spaces are interconnected as shown by the passage of blood cells between them. Collecting veins are seen in the pulp spaces at positions opposite to the arteriole entrance, receiving blood through end and lateral openings in their walls. The lateral openings are large enough in some instances to allow the passage

of several red cells abreast. The collecting veins are described as thin-walled structures randomly perforated with holes of varying sizes that are part of a branched-treelike arrangement. Although capillary networks supplied by an arteriole and feeding into veins are occasionally seen, there are relatively few of them. The capillaries are said to have holes in their walls through which blood enters or leaves the adjacent pulp space.

Parpart *et al.* report that they have never seen a venous sinus of the type described by Knisely (69), nor have they seen any activity in the venous pulp spaces that could be regulatory to the blood flowing through them. This is in direct opposition to statements by Knisely (71) and by Peck & Hoerr (94) regarding the regulation of blood flow through the splenic pulp. Knisely (71) took exception to the conclusions of Parpart *et al.* (93), particularly pointing out that their optical arrangements were such that not all structures present in the tissue would necessarily be observed. With the quartz rod, which Knisely used, it is possible to direct the light first one way and then another and thereby make previously unobserved structures visible (69).

In 1958, Snook (115), who believed one reason for disagreement concerning splenic circulation was the structural variability of the spleen among mammals, reported on fixed rabbit spleens. He had previously classified the mouse with mammals that had non-sinusoidal spleens (114), and comparative studies showed that the rabbit spleen was more nearly like human spleen than the other animals observed. Conclusions from his histological studies of the rabbit were that rabbit spleen had the open type of intermediate circulation, that white pulp capillaries occasionally connected directly with premarginal sinuses, and that penicillar branches terminated in pulp cords in ampullary dilatations.

In the 1958 edition of Bailey's *Textbook of Histology* (112) the authors take the stand that "there is a fairly direct connection from the capillary to the venous sinus in most cases, but the system is open in the sense that the lining membrane changes from endothelial cells to flattened reticular cells, and contains perforations through which erythrocytes may readily pass."

Fleming & Parpart (41) investigated the spleens of young rats and found them to be very different from mice. Capillary networks were seen which had a pattern very similar to that of mesenteric circulation (144). No venous sinus or pulp spaces were found.

Vascular walls were easily seen and very few red blood cells were free in the intercellular space.

Fleming and Parpart suggest that such a capillary pattern in the rat is an infantile characteristic and that pulp spaces develop when the animal becomes more mature. They believe that the fact that endothelial walls can be seen with such clarity in this preparation proves that they could also be seen, if present, in the spleens of mice. Thus the position taken by Parpart for an open system of intermediate circulation in the mouse spleen appears strengthened.

It is very difficult for an unbiased reader to decide in favor of one or the other types of circulation in the spleen because of the convincing arguments presented by the proponents of each. It has been suggested, however, that the burden of proof rests upon those who favor the open type of circulation, since endothelium is universally present in every other vascular system (26).

There are one or two structural arrangements described by Parpart *et al.* which would be unique if they do exist, i.e., capillary vessels with holes in their walls through which blood enters or leaves the adjacent pulp area, and veins which have end and lateral openings varying in size from 5 to 20 μ , the latter openings being randomly spaced along the endothelial lining of the veins.

Williams (139) expressed the opinion that the entire spleen might be thought of as a modified blood vessel with certain special structures in its lumen and, therefore, that the endothelial lining of the internal blood channels might have a different significance than elsewhere.

Microcirculation in the Lung

Microscopic observations of pulmonary circulation date back to Malpighi (84) in 1661. Occasional reports appeared in the literature from time to time after this, possibly the greatest concentration being in the 1930's.

In 1930, Olkon & Joannides (91, 92) studied the pulmonary circulation in dogs, frogs, and alligators! The optical magnification was quite low by present day standards (60 \times) and the fact that the animals were on artificial respiration and their lungs in constant motion must have added considerable difficulty to their investigation. They describe what appeared to be a large capillary lying between the walls of the alveoli from which many smaller capillaries were given off. They believed that the single large capillary surrounding the alveolus was most likely a capillary

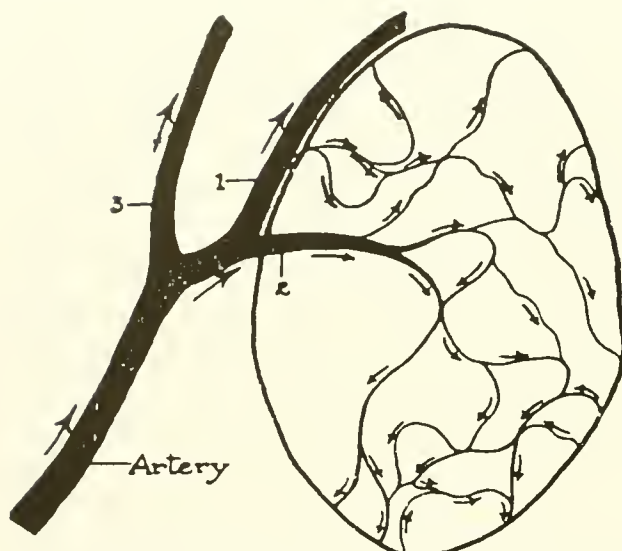


FIG. 17. Sketch of air sac and its vessels in the lung of a cat. [From Wearn *et al.* (128).]

network seen on edge. The smaller capillaries anastomosed frequently with each other and appeared to contract and relax.

In 1933, Daly (38) reviewed pulmonary circulation and briefly mentioned microscopic observations of pulmonary vessels, but these studies were concerned primarily with the response of small vessels to epinephrine. There were no papers in which normal vascular patterns were described.

Wearn *et al.* (128) introduced a method for the observation of minute vessels in the lung which utilized a quartz rod, for transmitting light, placed inside the chest cavity. The vessels were observed microscopically in the lung tip through a window in the chest wall. Observations were made on both moving and immobilized lungs. Arteriolar vessels showed pulsatile flow and steady flow, a different type of flow often occurring in two arteriolar branches from the same parent arteriole. Arterioles were seen to contract and relax, and reversal of the direction of blood flow was common. The walls of the capillaries were invisible, so that the caliber of the vessel and its course were determined by the column of blood it contained. Capillary vessels were seen to branch and anastomose frequently (see fig. 17). Wearn *et al.* report spontaneous opening and closing of capillaries, but the fact that the differentiation between arteriole and capillary was based on the number of blood cells which the vessel would accommodate (three or less for a capillary) throws some doubt on the validity of this statement. Also, the suggestion is made later in the report that intermittent flow in capillaries was

probably due to changes in the flow of arterioles from which the capillaries arose and that no proof of contraction of capillary walls was obtained. The capillary network, depicted by Wearn *et al.* as covering an alveolus, is very similar to that in many other sites.

The next detailed report of vascular architecture of the lungs appeared in 1954, when Irwin and his associates (66) published the results of microscopic observations on guinea pigs and rabbits. The technique used was that of transillumination with a quartz rod and oxygen insufflation to prevent respiratory movements. These investigators traced pulmonary arterioles to terminal pulmonary arterioles which branched to form capillaries. Blunt terminations of pulmonary arterioles, which lie in the septa between alveoli, gave rise to capillaries which then spread over several adjacent alveoli. Pulmonary capillaries were seen to be completely lined cylindrical tubes which branched and anastomosed to form intricate networks over the surfaces of alveoli. The capillary network was often supplied by several terminal arterioles and each network was drained by more than one venule. Arteriovenous shunts were found between a pulmonary arteriole and venule that ran side by side in an alveolar septum.

Additional observations by Irwin & Burrage (67) were that the diameters of arterioles and venules changed size when measurements of their walls were made over long periods of time, affecting the flow of blood. Alterations in the diameters of the arterioles were more marked than venular changes. Irwin and Burrage report that the walls of the capillaries covering an alveolus were seen to come together to obliterate their lumina. They suggest that, although the intermittent blood flow in pulmonary capillaries could be due to contraction of either arterioles or venules, the possibility of activity in the capillary walls must be considered. That capillary walls might contain contractile tissue, or that the endothelium lining the cells might swell to block the lumina are the possible means offered by the authors for causing intermittent flow in pulmonary capillaries.

A surprisingly small number of investigations of the normal vascular structures and flow of blood in microscopic pulmonary vessels have been carried out. However, Wearn's, diagrams (128) and the descriptions by Irwin *et al.* (66) of capillary networks covering alveoli indicate that this terminal vascular bed is made up of the same structural components with the same basic form as that of beds in other tissues and organs. Perhaps further investigations will explain the apparent closure of "capillary" walls seen by Irwin &

Burrage (67). The most likely explanation for intermittent flow through these minute capillary vessels is that the terminal arterioles and precapillary vessels which supply the capillary nets exhibit spontaneous vasomotion as seen in other areas.

Microcirculation in the Cochlea

The general pattern of blood vessels of the cochlea has been known for some time, the early descriptions being obtained from injected and fixed material. In general terms (40) the cochlea is supplied by the cochlear artery. This vessel enters the modiolus through the internal auditory meatus. The spiral ganglion has a rich supply of capillaries, and many arterioles find their way to the spiral ligament by way of the roof of the scala vestibuli. The stria vascularis is a rich network of small blood vessels with many anastomotic connections. The limbus has a capillary supply, and the tympanic surface of the basilar membrane often has a small arteriole running along it. Renewed interest in the blood supply of the cochlea in the past few years has resulted from applying microcirculatory techniques to this rather inaccessible site.

The capillary networks of several portions of the cochlea have been studied in detail. The areas so studied include the spiral ligament, a projection of thickened periosteum lying on the outer wall of the osseous canal of the cochlea; the spiral prominence, a slight ridge which projects into the cochlear duct; and the stria vascularis, the part of the spiral ligament lying on the outer wall of the cochlear duct between the spiral prominence and the vestibular membrane.

Two papers by Smith (110, 111), which contain a

detailed description of cochlea blood vessels obtained from fixed material, will be considered before discussing *in vivo* preparations. Investigations of capillary beds following intravascular precipitation of Prussian blue or lead chromate in the cochlea of guinea pigs, cats, and humans were carried out by Smith. She felt that while large features of the circulatory patterns had been adequately demonstrated, the capillary beds had been indistinctly shown and no attempts had been made to locate them precisely in relation to various portions of the inner ear.

In these studies, the radiating arteriole was found to ramify into terminal branches before entering the spiral ligament. In the cat and guinea pig four groups of small vessels, depending on their location and the course which they took, were designated by Smith. The first group was the network of the upper spiral ligament, group two was in the stria vascularis, group three was found in the spiral prominence, while group four was formed by the capillaries of the lower portion of the spiral ligament. In human labyrinths a fifth group, straight vessels in the thicker portion of the spiral ligament, was included in the classification (see fig. 18). The network in the upper spiral ligament is described as follows: Small branches from the radiating arteriole or one of its terminal ramifications have a winding course in a spiral direction usually above the attachment of Reissner's membrane. These small branches are seen to anastomose with other tributaries. They leave the upper spiral ligament by turning downward to the thicker part of the spiral ligament where they join venules, or they may turn upward and go through the bone wall to end in a collecting vein. The capillaries in the second group, the stria vascularis, are extensively connected with

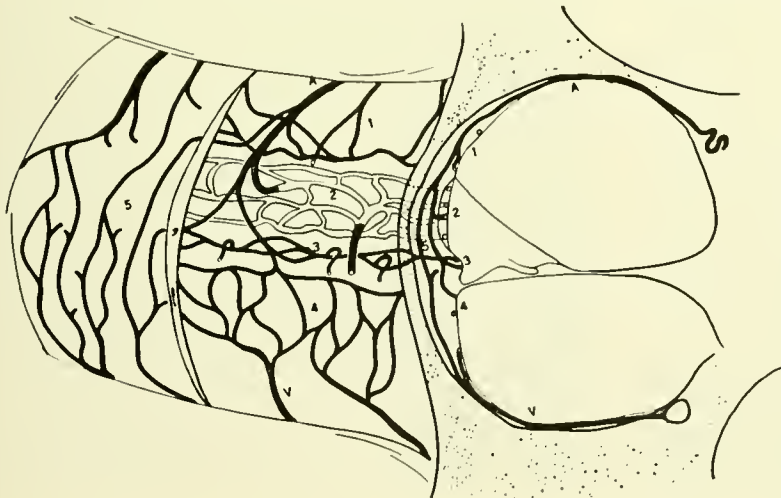


FIG. 18. Schematic drawing showing typical distribution of small blood vessels in the spiral ligament of the human cochlea. [From Smith & Giovacchine (113).]

one another and give the appearance of a network superimposed upon the deeper vessels of the spiral ligament. The superior and inferior borders appear straight and parallel. A large venule drains the network, formed by the junction of three or four stria capillaries. The venule turns backward and leaves the stria vascularis in its lower half where it descends peripherally, sometimes joined by other venules before entering into the collecting venous system at the lower edge of the spiral ligament. The blood supply of the spiral prominence, the third group, is different in the guinea pig from cat and man. In the guinea pig a single vessel is found near the epithelial layer, with perhaps a single layer of connective tissue cells interposed. The vessel courses parallel to the network of the stria vascularis just below its inferior border, although no vessel of the spiral prominence is ever connected to the network of the stria vascularis. At times the vessel is double, with the duplicate vessel running under the edge of the stria vascularis. The venules join the collecting venules of the lower spiral ligament. In the human, the vessels in the spiral prominence form a separate, narrow, rolled network below the stria vascularis, supplied by large arteriolar vessels and drained by large veins. Small vessels leave the network by turning upward and laterally into the spiral ligament before emptying into veins. They also may enter venules in the lower spiral ligament.

The capillary network in the lower spiral ligament is also supplied by direct large arteriolar branches. These arteriolar branches descend close behind the stria vascularis and terminate in a spiral vessel in the crest of the spiral ligament. Branches are given off to the stria vascularis and spiral prominence on the way. The spiral vessel marks the upper limit of a network which originates from it. Where the spiral ligament is quite thin, the network can be seen as a loose mesh of vessels under the mesothelium of the scala tympani.

The fifth group found in the human is made up of straight vessels found in the connective tissue between the scalae and the bone. They show variations in size and structure, and course directly from arteriole to venule. Some seem to be capillaries, being devoid of perivascular cells, while others are larger and may represent a type of arteriovenous shunt.

The radiating arteriole was found to have both longitudinal and tangential smooth muscle cells and a thin adventitia of two or three layers of connective tissue cells. Capillaries were composed of endothelial cells and infrequent smooth muscle cells. The capil-

laries of the stria vascularis were composed only of endothelial cells, although occasionally a perivascular cell was seen. It could not be determined whether it was a smooth muscle cell or not. The large draining vein was seen to have a few smooth muscle cells arranged transversely or tangentially.

Smith concludes that the human cochlea shows a definite arteriolar supply to the various vascular groups of the spiral ligament. There are several distinct capillary networks rather than one large continuous field, and these networks are separated by their vascular supply and drainage. She suggests that such a vascular pattern makes it possible to have regional circulatory variations within a small segment of the spiral ligament.

In 1954, Weille *et al.* (131, 132) published two papers describing the circulation in the spiral ligament and stria vascularis of the living guinea pig. The cochlea was first exposed and then microscopic fenestration of either the apical or third cochlear turn was carried out. The vessels observed included arterioles, arteriovenous anastomoses, capillaries, and venules of the spiral ligament and the capillary network of the stria vascularis. Capillaries of the spiral ligament formed an intricate network of dividing and anastomosing vessels fed by arterioles. Arteriovenous anastomoses were formed as a branch of an arteriole that entered a venule with no intervening capillary network. The capillaries of the stria vascularis formed a network of branching and anastomosing vessels that emptied into the venules of the spiral ligament.

All arterioles, arteriovenous anastomoses, and venules contracted and dilated independently. The rate of blood flow varied in each vessel from time to time, going from very rapid to no flow at all.

A more detailed description followed (65), in which it was reported that there were two distinct types of tiny vessels, one in the area of the upper spiral ligament and the other in the area of the pigmented cells (the cochlear duct). Branching and anastomosing were frequent in these networks. Both received blood from the arterioles and both drained into the venules in the area of the cochlear duct.

Collecting venules, into which the capillaries drain, pass transversely through the area of the cochlear duct, and drain into the venules which are perpendicular to them and lie outside this area.

Vessels which ran from arterioles to venules were seen to give off capillaries, but no capillaries were seen to re-enter them. For this reason they were called arteriovenous anastomoses rather than met-

arterioles, a name given to them by Seymour (109). The anastomoses were seen to contract to complete closure.

Microscopic observations of cochlear blood vessels in living guinea pigs were reported by Perlman & Kimura (95, 96) in 1955. Special attention was given to the small vessels of the spiral ligament and the stria vascularis. The quartz rod technique was used after the cochlea was fenestrated in the fourth turn. The fenestra was 0.1 to 0.2 mm² and exposed the spiral ligament on the lateral wall of the cochlear duct as well as the stria vascularis. Perlman and Kimura were certain that all vessels in the field were visible to them and that all the basic units of a vascular bed were present. The identification of the various components was based on the diameter, the wall thickness, shape of the vessels, the rate and direction of flow, and the presence of smooth muscle cells and vasomotion. Numerous anastomoses between all types of vessels were seen, but the distribution and direction of flow from the radiating arteriole to the collecting venule suggested a segmental blood supply.

The arterioles of the spiral ligament were seen to branch into a number of different vessels. A small branch at right angles to the radiating arteriole was seen to run parallel to the cochlear duct in the upper portion of the spiral ligament. It anastomosed with a similar vessel from an adjacent arteriole.

Another branch was seen that crossed the underlying stria vascularis and emptied into the collecting vein below the cochlear duct. This type of vessel, regularly seen in the area, has no branches, is narrow and straight, and has a rapid blood flow. It has

smooth muscle cells regularly distributed along its walls. The authors have called this vessel an arteriovenous arcade. (See figs. 19 and 20.)

Another branch of the radiating arteriole with a uniform diameter extends over the underlying stria vascularis, has no branches, and ends at the level of the spiral prominence just below the stria vascularis. The vessel with which the branch connects runs parallel to cochlear duct and tributaries from it join collecting venules of the spiral ligament. The blood vessels in the stria vascularis are at right angles to the radiating arteriole, the collecting veins, and the arteriovenous arcade.

The last branch from the radiating arteriole is the one which enters the stria vascularis. Diameters of the stria vessels are usually larger than the diameters of the radiating arteriole or arteriovenous arcades. Stria vessels do not have a regular distribution of smooth muscle cells and were not seen to contract.

The vessel in the spiral prominence is independent of the stria vascularis, being directly supplied by a branch from the radiating arteriole. A large number of tributaries leave this vessel to join the collecting vein. Anatomically, it seems to have the qualifications of a capillary, being small in size and devoid of smooth muscle cells, and having a slow rate of blood flow. It shows no vasomotion.

In commenting on the vascular pattern, Perlman and Kimura state that the segmental type of blood flow suggests that interference with function may be localized. Interruption of flow in a radiating arteriole of an arteriovenous arcade may occur while flow continues in the underlying stria vascularis. Flow in the stria vascularis may cease while active flow continues in the radiating arteriole, arteriovenous arcade, spiral prominence vessels, and venules. The presence of arteriovenous arcades in the spiral ligament suggests a possible regulatory mechanism for controlling flow in the stria as well as affording anastomotic channels to insure continuity in blood flow along the spiral ligament.

Perlman believes that the stria vessels, the arteriovenous arcade, and the spiral prominence vessels have functional roles. The stria vessels may be called capillaries with regard to their position, the fact that they have the lowest blood flow rate, and the fact that they have no smooth muscle cells in their walls. The decrease in the rate of blood flow from the radiating arteriole to these capillaries of the stria vascularis is large and abrupt. The final exchange of diffusible substances probably occurs in these vessels.

The role of the cochlear blood vessels in the absorp-

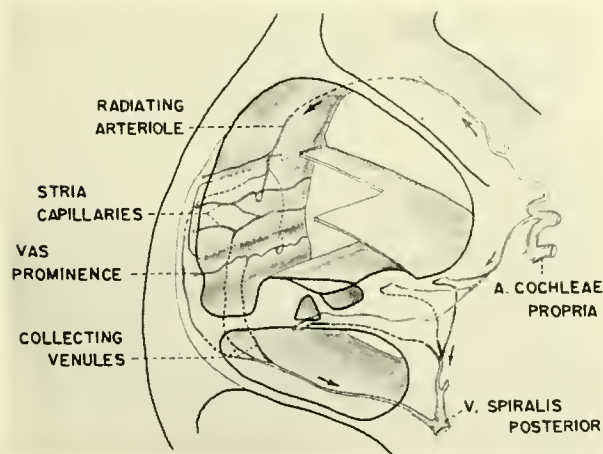
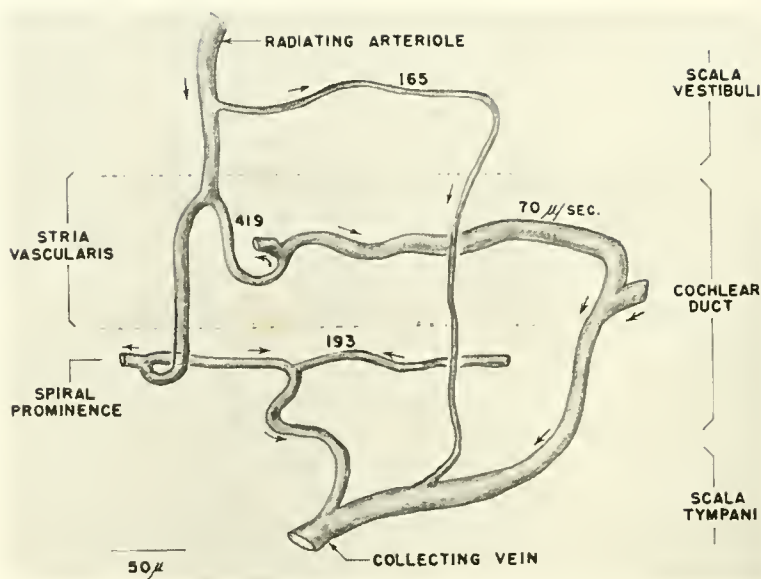


FIG. 19. Segment of cochlea showing relation of exposed vessels to the cochlear duct and the main trunks in the modiolus. [From Perlman & Kimura (95).]

FIG. 20. Schematic drawing showing relations of basic vascular units exposed by the fenestra and the average blood velocity in micra per sec. [From Perlman & Kimura (95).]



tion and secretion of perilymph and endolymph is still not clear, although it is believed that endolymph is secreted by the stria vascularis (40). It is interesting that this fluid, which fills the scala media, differs in ionic content from perilymph which fills the scala vestibuli and the scala tympani. Unlike all other extracellular fluids in the body, endolymph is high in potassium and low in sodium, thus more nearly resembling an intracellular fluid. The very slow rate of blood flow in the stria vascularis may be necessary to allow the formation of this intracellular-like fluid.

It has been suggested, also, that the slow flow rate and the absence of vasomotion in the stria vessels contribute to the fact that blood flowing through the cochlea is not heard.

Preferential or Thoroughfare Channel

The attempt to give a representative description of vascular patterns in terminal vascular beds has not escaped the usual criticisms aimed at generalization from one animal to another or among different tissues within the same animal. One of the major issues among investigators of the microcirculation has been the acceptance of a preferential channel as a component of all capillary networks. A chronological presentation of the development of the concept, the modifications, and current status might assist in clarifying the issue.

The first description of the arteriovenous (a-v) bridge, later to be called the thoroughfare or preferential channel, appeared in 1937 (143). Zweifach, in studies of the mesentery, nictitating membrane,

and undersurface of the tongue of the frog, described two types of vessels present in these structures. One was a continuous central trunk that connected an arteriole and a venule. This vessel, a direct continuation of an arteriole, was invested with widely separated atypical smooth muscle cells which were less responsive to mechanical stimulation than smooth muscle cells of the arterioles. The a-v bridges did not always take a direct linear course from the arterial to the venous side, but appeared in three basic patterns: 1) a direct course without other terminal branches, 2) a fountain-shaped pattern, 3) a horse-shoe-shaped pattern, which was to become regarded as the basic design for the preferential channel. The a-v bridge was functionally different in that it always had a patent lumen with uninterrupted blood flow. The second type of vessel was the true capillary, a nonmuscular vessel which was an off-shoot or branch from the a-v bridge, not in the direct path of blood flow from arteriole to venule. In a camera-lucida drawing of the vascular pattern in the frog mesentery it can be seen that the a-v bridge either formed a loop to return to the venule accompanying the arteriole from which it arose, or continued across the capillary bed to join another venule (fig. 21).

In a second paper the same year, the arteriovenous bridge was reported in the mesentery and ear of the mouse (150). In 1939, Zweifach (144) extended his studies on living vessels in the mesentery, tongue, skin, and intestinal wall of the frog, and in the mesentery and ear of the mouse. Little new information was added, but the functional significance of the a-v bridge was stressed. The main central pathways were

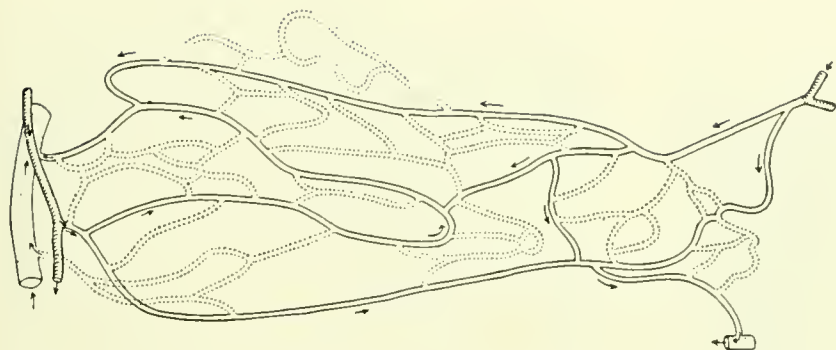


FIG. 21. Camera-lucida outline of vessels in the capillary bed of the frog mesentery. [From Zweifach (143).]

said to have a vigorous circulation even when tissues were in a resting or anemic state. The bridge was regarded as a muscular capillary and was the central pathway from which the remainder of the capillary vessels were distributed as side channels.

In 1944, Chambers & Zweifach (20) collaborated on a paper in which the studies were confined to the mesenteric circulation in the dog and the rat. They state that the fundamental architecture is the same for both tissues. The mesoappendix of the rat differs from other parts of the mesentery in its lack of any major vessels coursing from the aorta or to the vena cava, all vessels in the mesoappendix being less than 80 to 100 μ in diameter. The description of the capillary bed is based primarily on observations in the mesoappendix of the rat, in which the a-v bridge is a prominent structure. The term "metarteriole" (Gr. meta—beyond) is introduced to designate the proximal contractile portion of the central channel. Beyond the metarteriole, muscle cells disappear and the channel continues as the a-v capillary until it joins a venule. Other contractile muscle cells, designated precapillary sphincters (the precursors of the true capillary), were found at the proximal end of the channel but were absent at the venular end. Each central channel and its side branches with their interposed true capillaries were said to constitute a structural unit. In a summary in 1946, Chambers & Zweifach (21) state that the basic topography of a predominantly nutritive type of capillary bed is presented as a central channel of which the true capillaries are side branches. The different portions of the central channel, in sequence, were the metarteriole which exhibits vasomotion and has typical but discontinuous muscle cells; the proximal portion with atypical muscle cells; the distal portion with no muscle cells; and the nonmuscular venule. The precapillaries were described as the proximal muscular portions of the abrupt offshoots of the muscular portion of the central channel, acting as sphincters and

controlling blood flow through capillaries. The true capillaries continue from the precapillaries and are also direct branches of the distal portion of the central channel and of the nonmuscular venule.

In 1947, the functional aspect of the structural unit was again emphasized (22). It was pointed out that in some tissues which maintain a constant level of flow volume there is no discernible organization of capillaries, while in tissues such as the muscular system and the gastrointestinal tract with varying activity the structural unit exists. This vascular pattern allows for great expansion in the number of vessels with an active circulation at one time and restriction of flow to the preferential channel during a period of inactivity. In the decade following the introduction of the preferential channel, new ideas and new terminology were added. For clarification of the structure and function of the terminal vascular bed in the rat mesentery, excerpts from a paper by Chambers & Zweifach (22) follow. "The preferential vessels have been termed thoroughfare or a-v channels. The proximal portion of these channels, termed metarterioles, together with their precapillary sphincteric offshoots, are muscular and spontaneously undergo periodic changes in caliber. This type of movement has been termed vasomotion, a slow intermittency of partial relaxation and constriction at intervals of about 30 seconds to 3 minutes. . . . The precapillary sphincteric offshoots lead into an interanastomosing system of true capillaries (devoid of muscle elements) which constitutes the bulk of the bed. The capillaries rejoin the distal continuation of the thoroughfare channels through inflowing tributaries." The thoroughfare channels, always open, are said to maintain a constant pressure relationship between their arteriolar and venous ends, the flow of blood through them being more rapid than through other vessels in the bed. The channel is said to be the site of outward filtration, while inward filtration occurs in the true capillaries.

One significant anatomical difference noticed in comparing microphotographs of circulatory patterns in the rat mesoappendix with that of other tissues is the absence of paired arteriole and venule in the mesoappendix of the rat. An arteriole emerges singly from its parent vessel, descends into the mesentery, then forms a loop which in its return is joined by other capillary vessels before emptying into the vein which accompanies the artery of origin. In most vascular beds, other than the mesentery, arterioles and venules are found to be adjacent and to branch together until the final ramification which forms the capillary net. The small arterioles, from which the true capillaries arise, form arcades or arcuate patterns with other arterioles rather than continuing as a direct pathway to the venous side. It is not uncommon to see, in the bat wing at least, a short terminal arteriole that quickly joins a collecting venule after giving off one or two branches (see fig. 22). Contrary to the description given to preferential channels these terminal arterioles will close down completely or may be devoid of blood when their parent vessel is occluded by contraction of the circular smooth muscle which invests them.

According to subsequent papers by Zweifach (146, 147) and Zweifach & Metz (151, 152), in which vascular patterns are compared, it seems that the preferential channel occurs mainly in rat mesentery, outer edge of rat skeletal muscle, and the serosa of the small intestine of the same animal. He states that the preferential channel is unusually prominent in the mesentery but is not a major structural feature of the urinary bladder and the skin. Further reservations as to the ubiquitousness of the preferential channel have appeared as a result of observations in the under surface of the skin, the skeletal muscle, urinary bladder, several mesenteric structures, and the serosal surface of the small intestine. Zweifach states that "a major variable lies in the structural organization of

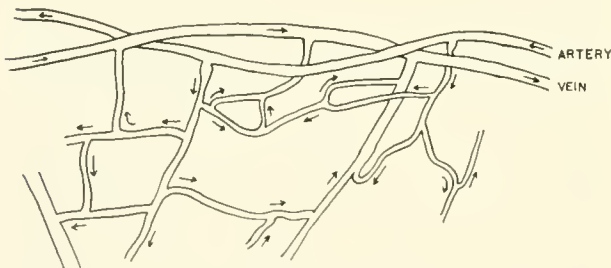


FIG. 22. Arteriovenous pathways in the subcutaneous area of the bat wing.

the different vascular beds, especially the mode of distribution of the capillary system from the arterial vessels. In such tissues as skin and intestinal wall, the majority of capillaries originate as direct offshoots of larger arteries and arterioles. The distal ramifications of the arterioles have relatively few capillary offshoots and usually terminate by interconnecting freely with one another in a series of arcades. This is in direct contrast to the mesentery where the arterial subdivisions, the metarterioles, serve as the parent stem from which the precapillaries and capillaries branch out."

Other investigators who have found thoroughfare channels in various tissues include Lutz *et al.* (82), who confirmed their presence in frog mesentery but failed to identify them in the hamster cheek pouch or retro-lingual membrane of the frog. Baez (6) reports a short arteriole which turns inward to become a draining venule, thus forming a thoroughfare channel in the muscular coat of the small intestine. Staple & Copley (118) describe a thoroughfare channel in the labial marginal gingiva of the mandibular incisor of the hamster. Lee & Holze (77) observed the thoroughfare channel in the human conjunctivae, and Lee & Lee (78) describe the structure in the mesentery of the guinea pig.

The preferential or thoroughfare channel, either as a structural or functional unit, has not been seen in some areas which have been subjected to extensive study by various microcirculatory investigators. Nicoll & Webb (88) report that there are no preferential pathways in the subcutaneous tissues of the bat's wing. Clark & Clark (29) do not report them in the rabbit ear. Grafflin & Bagley (55) found no such structure in the frog web and urinary bladder, nor in the human conjunctivae. Later, Grafflin & Corddry (56), reporting a more detailed study on the bulbar conjunctiva of man, described vessels between arterial and venous channels, arteriovenous communications that seem similar to the preferential channel.

It would seem then that the preferential channel should not be considered as a component of a typical capillary network. Although it is possible to demonstrate a similar anatomical arrangement in terminal vascular beds other than in the mesentery, there is no confirmation of the existence of a preferential channel on a functional basis. It is possible that such a flow pattern is necessary for the relatively avascular mesentery, and therefore constitutes a special rather than a typical entity of microcirculation.

Arteriovenous Anastomoses

A detailed and comprehensive review by Clark (23) in 1938, dealing with arteriovenous anastomoses, obviates the necessity of reporting individual investigations up to that time. The discussion here is mostly confined to the results of *in vivo* studies.

A direct connection between arteries and veins by passages through which blood is carried without interchange with extravascular fluids had been described repeatedly since the early 1800's. Such passages were then considered to be rare, occurring as a result of injury or as a developmental anomaly. Their presence in the ear of the living rabbit, as demonstrated by Clark & Clark (29, 30) and Grant (57), established their existence in the normal vascular bed.

Grant (57) concluded from his observations of reactions of these vessels that arteriovenous anastomoses were important in regulating body temperature. Responses to heating the animal indicated that when the body temperature was elevated, dilation of arteriovenous anastomoses permitted a large amount of blood to flow through the ear, thereby increasing heat loss. Constriction of arteriovenous anastomoses occurred when the animal was cooled and thus heat was conserved. This concept was extended in studies of the toes of birds and the fingers and toes of man (58).

Clark & Clark (30) studied the arteriovenous anastomoses in transparent chambers in the rabbit ear with observations over long periods at high magnifications. High magnifications made possible the descriptions of structural components. Many arteriovenous anastomoses are present in the ear of the rabbit, with considerable variations in their arrangement. Some arise directly from the central artery of the ear, others from secondary or smaller branches, and some form the termination of an artery or arteriole. Most of these, however, arise from small arterial branches. They all empty primarily into larger veins (see fig. 23).

As to the structure, arteriovenous anastomoses are found to be straight or coiled, with a thick muscular wall on the arterial side and a thinner, funnel-shaped widening on the nonmuscular venous end. Variations from this general pattern include the absence of the funnel-shaped venous end and a continuous muscular wall throughout the entire vessel. The narrow intermediate portion has a wall of extra thickness which seems to be the most contractile portion. The venous portion is noncontractile, but the large veins with which the communicating vessel connects often have substantial muscle walls and show definite contrac-

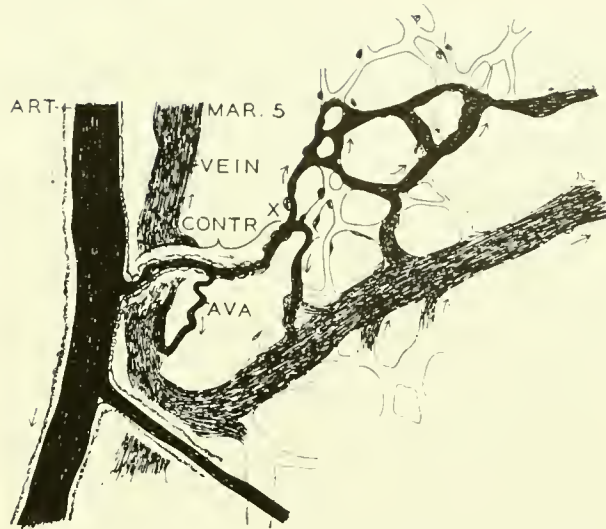


FIG. 23. Camera-lucida drawing of a plexus of regenerated vessels in the rabbit ear. [From Clark & Clark (34).]

tility. Most of the cross connections show inside diameters of 20 to 40 μ during dilatation. Typical anastomoses may be as small as 5 μ in diameter or as large as 40 μ .

Arteriovenous anastomoses are more active than arteries and arterioles and show a greater tendency for independent action. They contract and dilate spontaneously and periodically, but with a rhythm independent of either neighboring anastomoses or even of the artery from which they arose. They generally contract more rapidly than arteries, both rhythmically and in response to stimuli.

Clark (23), did not attempt to explain the function of the arteriovenous anastomoses, but felt that it was significant that they occur normally in greatest numbers at sites most frequently subjected to mechanical and thermal irritations, the kinds of stimuli which produce prolonged dilation of arteries and arterioles.

From his observations of the frog mesentery, Zweifach (143) describes short arteriolar-venular anastomoses between vessels only slightly larger than capillaries. These short channels effectively divert arterial blood directly into veins. Their caliber changes seem related to the activity of the capillary circulation. When most capillary vessels are open and have active blood flow, the arteriolar-venular anastomoses remain closed, and then open when capillary circulation decreases. The anastomoses differ in this respect from arteriovenous bridges which maintain a relatively fixed diameter. Arteriolar-venous anastomoses in the mesentery of the mouse were described as short, tor-

tuous vessels that never branched and were not part of the capillary bed.

Later, similar vessels in the rat mesoappendix were described (20). The connecting passages in that tissue join a metarteriole with a neighboring venule, or an arteriole with a venule. They are muscular for about two-thirds of their length from the arterial end. When such shunts dilate, blood flow ceases in the arterial components distal to the shunts.

Direct microscopic observations in other tissues of living animals have revealed arteriovenous anastomoses. Wakim & Mann (124) carried out microscopic studies on the liver of frogs and various mammals at magnifications up to 600 times, utilizing the quartz rod transillumination technique. They found arteriovenous anastomoses in all animals studied. They saw anastomotic connections between the interlobular branches of the hepatic artery and the portal vein in both amphibian and mammalian livers. Seneviratne (108) observed blood vessels of the livers of frogs, mice, and rats, and described similar anastomoses. For frog liver he described several phenomena. Many short branches from a hepatic artery enter the accompanying portal vein. Arterioles cross a lobule and enter a portal vein on the other side. Occasionally the arteriole enters a hepatic vein. Small arterial branches pass through the liver and anastomose with subcapsular arteries. In the mouse and rat many types of anastomoses occur between arterial and venous vessels, the commonest being a direct communication by short branches between the hepatic artery and the accompanying portal vein.

Irwin & MacDonald (64) studied guinea pig livers using the quartz rod technique and found the vascular bed to be similar to that described for the liver by Knisely *et al.* (72). The Knisely group found connections between hepatic arterioles and portal venules which they called arteriportal anastomoses. Bloch (14) described arteriportal anastomoses (APA) as being completely lined smooth-walled tubes that connect hepatic arterioles with portal venules at irregular intervals. The hepatic arteriole winds itself around the portal venule and then sends short branches out to form APA.

Parpart *et al.* (93) describe arteriovenous anastomoses in the spleen of the mouse as seen by microscopic observation. There, about one artery in ten makes direct connection with a collecting vein. An arteriole may anastomose with a collecting vein at any point on the vein, lateral connections occurring more frequently than end-to-end anastomoses. When the connection is lateral, the arteriole is perpendicular

to the venous wall. In the end-to-end anastomosis, the arteriole gradually widens to become a collecting vein.

Poor & Lutz (97) found no arteriovenous anastomoses in the hamster cheek pouch. Irwin *et al.* (66) found arteriovenous shunts in the lungs of guinea pigs and rabbits, although they appeared infrequently. Blood flow through the shunts was unidirectional, going from arteriole to venule. Blood flow through arteriovenous anastomoses in the bulbar conjunctiva has been described by Bloch (15). Weille *et al.* (132) saw them in the stria vascularis.

Zweifach (148) has said that there is little doubt that occasional shunts between arteries and veins exist in almost every tissue in the body, but are not a prominent feature of most tissues. He further suggests that pathways, not distinct anatomical shunts, go from arterial to venous systems allowing blood to bypass the capillary network. Communications between arterial and venous vessels occur more frequently in terminal vascular beds than in more proximal portions.

It does not seem necessary to assign any highly specialized function to arteriovenous anastomoses, such as heat regulation, although this is still done (39, 98). Folkow (44) is of the firm opinion that arteriovenous anastomoses in the skin are specialized structures predominantly engaged in regulation of heat loss and are regulated by their own constrictor fibers. His evidence, while convincing, is indirect. Van Dobben-Broekema & Dirken (121, 122), in a study of the reaction of rabbit ear vessels to heating, offer evidence that there is no obvious relationship between the temperature of the ear and the diameter of the arteriovenous anastomoses. Zweifach (148) mentions the possibility that selective vasoconstriction may reduce capillary circulation and cause blood to be shunted through passages which would offer the least resistance to flow from the arterial to the venous side.

The information derived from the above investigations indicates that terminal vascular beds of most tissues are supplied with short communicating vessels between arterial and venous systems. These arteriovenous connections allow arterial blood to be shunted into the venous system without first passing through a capillary network. As Zweifach (148) has suggested, the shunts may be preferentially in use when vasoconstriction of small arterial vessels beyond the shunts increases resistance to flow. Arterial blood would then be diverted through shunts which afford the path of least resistance. The selective vasoconstriction to which Zweifach refers might result from the response of terminal arterioles or precapillary sphincters to

changes in the local environment, and thus whether or not blood flowed through capillary networks would be determined by the immediate needs of the tissue. Thus, no complex central nervous control is necessary, if the postulate that terminal vasculature is primarily under the control of local conditions is acceptable.

BLOOD FLOW THROUGH TERMINAL VASCULAR BEDS

Capillary Contractility

Ideas regarding contractility of capillary vessels have come full circle, beginning and ending with the concept that capillaries are noncontractile and the blood flow through them depends on contraction or dilatation of the arterioles which supply them. During the intervening periods, investigators have promoted the concept of independent contractility of capillary vessels, first believed to be brought about by the contraction of perivascular or Rouget cells and later thought to be due to the contraction of endothelial cells. At present it is generally accepted that true capillaries do not contract. By definition they are devoid of muscular elements, so that muscular contractility is out of the question, and the endothelial cells of which they are composed are also noncontractile. The internal diameter of capillaries may vary, however, by passive response to changes in pressure or in the size of the endothelial cells which form the basic structure of their walls.

Independent contractility of capillaries was a controversial subject in the eighteenth century. The opinion expressed by Haller (60) in 1756 that capillaries did not contract was generally accepted by most physiologists until early in the twentieth century [(54), see also (87)]. At this time publications by August Krogh (73) appeared. Krogh's belief that capillaries really contracted is found in a description of an experiment in his book "which demonstrates in a crucial manner that the whole length of a capillary from an arteriole to a venule can be contractile, that it cannot, when contracted, be forced open by the available arterial pressure. . . ." Krogh was convinced of the independent contractility of capillaries but he also believed that no evidence obtained thus far was conclusive enough to explain the mechanism by which this was carried out.

Two possible means of decreasing the diameter of capillary vessels had been suggested. One was that either osmosis, or imbibition by endothelial cells, was

responsible, and the other was that active contraction of extraendothelial cells occurred, as described by Rouget (103) in 1873. Krogh believed that the imbibition theory was ruled out by data published by Steinach & Kahn (119), showing that the outside diameter of contracting vessels decreased, rather than remaining constant or increasing as it would if the endothelial cells enlarged. He believed that anatomical proof was lacking to establish the functional role of Rouget's cell. Because of this need for more histological information, he encouraged Vimtrup to conduct a detailed study of the structure of the capillary wall. Vimtrup (123) examined stained sections of frog tongue and found cells such as those described by Rouget. He subsequently named them Rouget cells. He was also successful in identifying these cells on living minute vessels in the tail of newt larvae, and in seeing them contract. The frequent spontaneous contractions and dilatations of vessels seemed to occur at the location of the nucleus of a Rouget cell. This was final proof for Krogh that capillaries possessed independent contractility, the contractile element being the Rouget cell. He explained away the conclusions of the Clarks (27, 28) that the Rouget cells were noncontractile by saying that there was no proof that the cells they described on vessels in tadpole tails were the same as Rouget cells or that the contractions they saw were similar to normal contractility. Krogh, convinced that the controversy regarding capillary contractility was settled, extended his belief in the Rouget cell to include its occurrence on all capillaries in both Amphibia and mammals.

In a very short time, however, the concept of the Rouget cell as a contractile cell controlling the diameter of capillary vessels was challenged by detailed studies on small vessels in the rabbit ear, a technique introduced by Sandison (104) in 1924, and used by him and the Clarks, in whose laboratory he began his work. A chamber for the rabbit ear was perfected in which original vessels as well as newly formed ones could be watched for many months. In 1931, Sandison (105) reported that the appearance of Rouget or adventitial cells on newly formed vessels occurred in a few hours. Using a magnification of 400 times he could find a clear space between these cells and the vessel wall or an endothelial nucleus. The cells did not remain fixed, but wandered along the vessel wall. Sandison stated that the function of the Rouget cell was obscure, except that it helped form a supporting framework for the vessels. He was able to demonstrate in the rabbit ear vessels that a widening of the space between the adventitial cell and the arteriolar wall

occurred when the arteriole narrowed. Clark & Clark (27) had previously made a similar observation in Amphibia, and also had observed that the contraction of small vessels on which no adventitial cells developed was the same as those in which adventitial cells were present. These observations seemed to rule out any possibility that the adventitial or Rouget cell was responsible for contraction. Sandison also noticed that, as newly formed vessels changed from capillary to arterial forms, the adventitial cells disappeared and circular smooth muscle cells took their place. It was shown later by Clark & Clark (33) that adventitial cells actually differentiated into smooth muscle cells as new capillaries developed into arterioles.

A year later Sandison (106) stated that it was clear from continuous microscopic observation of minute vessels that contraction and relaxation of smooth muscle cells of arteries and arterioles were responsible for alterations in blood flow through capillaries, and that neither Rouget cells nor endothelial cells played any part in contraction of vessels.

In the same year, Clark & Clark (29), after observing capillaries of normal ear tissue through a transparent chamber, stated that if any capillary contractility did occur it was too negligible to have any influence on the circulation. In subsequent papers Clark & Clark (33, 34) summarized the accepted ideas regarding capillary and endothelial contractility as follows: *a)* Studies on mammalian vessels in transparent chambers, where details of the cellular structures could be clearly seen in unanesthetized animals, gave no evidence for any contractile power of either endothelial or adventitial cells. This view was supported by other investigators (61, 101, 102). *b)* The real factors responsible for the control of circulation in the minute vessels of the mammal are smooth muscle cells on arteries, arteriovenous anastomoses, and large veins (105). *c)* No contractile activity is seen in mammalian capillary endothelium (29, 31, 33, 86), although definite active spontaneous contractions occur in the capillary endothelium of Amphibia (28, 142, 143). They point out that the experimental evidence for contractility of mammalian capillaries was based, in some instances, on studies of nontransparent regions in which the structure of the wall of the minute vessels and their true diameters could not be seen. Therefore, conclusions as to whether they were contracted or dilated could only be inferred from the number of red cells present in them. Also, belief in contraction of mammalian capillaries was often based on observations of amphibian vessels in which contractions had

been seen to occur with and without extra-endothelial cells.

In spite of overwhelming contrary evidence, some investigators still held for a time to their belief in capillary contractility. It seems unnecessary to review the disagreements in the face of the general acceptance at the present time of the opinions originally expressed by Sandison (106) and extended by Clark & Clark (29). If one accepts the definition of a capillary as a nonmuscular endothelial tube between the arterial and venular systems, one may state unequivocally that mammalian capillaries are noncontractile.

Nicoll & Webb (88) stated that observations on capillaries in the bat wing showed that no perivascular cells, such as Rouget cells, existed in the region of these vessels. The smooth muscle cells, at the transitional points from the terminal arteriole to the capillary, end rather abruptly. Beyond the termination of smooth muscle cells within the walls no change in the diameter of the capillaries, due to activity of perivascular cells, has been observed.

The question of the role played by the endothelial cell in caliber changes in capillaries is more unsettled. To cite some of the recent descriptions of endothelial cell activity, Nicoll & Webb (88) reported modifications in capillary diameter that may result from elastic recoil of the endothelial wall due to pressure variations either inside or outside the vessel. The caliber change is due neither to active contraction of the endothelium nor to intracellular swelling. Later, Webb & Nicoll (130) pointed out that loss or gain of fluid through the walls of endothelial cells may result in apparent changes in their size. Also, since capillaries are distensible, they may show deformation under variable conditions (89). These responses are usually slow in their development and give no indication of active participation by the endothelial cells. Chambers & Zweifach (21) believe that slow spontaneous endothelial responses for the most part represent accommodation to changes in pressure; that endothelial cells possess a cellular tone which gives a degree of elasticity to the capillary wall. Lutz *et al.* (82) found that endothelium did not respond to mechanical stimulation.

Folkow (44) summarizes current opinion in stating that "slow swellings of the capillary endothelium are sometimes observed, but are more probably to be looked upon as passive osmotic effects or deformations due to passive luminal changes, caused by variations in intravascular pressure."

Vasomotion

The word "vasomotion" has had extensive use since its first appearance in 1944 (20). The term was used at this time by Chambers and Zweifach to describe the spontaneous contractions and dilations of small arterioles (metarterioles) and the muscle cells of their branches (precapillary sphincters) in the rat mesentery, also called mesoappendix. It has subsequently come to be used to indicate observed diameter changes of any blood vessel.

Reports of variations in the caliber of small blood vessels have been in existence for almost as long as microscopic studies of them have been carried out. Special interest in this phenomenon was shown during the period of controversy over capillary contractility. In the years following the introduction of the rabbit ear chamber for microscopic observation of small blood vessels, numerous papers appeared in which spontaneous alterations in small blood vessels were described. Clark & Clark (29) spoke of the normal occurrence of spontaneous rhythmic contractions of arteries down to their smallest branches. Different arteries and parts of arteries were seen to contract at different rates (30). Sandison (106) reported rhythmic contractions of arterial vessels but saw no active contractions of veins or venules. Clark *et al.* (35) believed that an intact nerve supply was necessary for spontaneous contraction of the arterial vessels. Numerous other investigators reported periodic alterations of small vessel diameters (17, 57, 62, 141).

Chambers & Zweifach (20) described vasomotion in terminal arterioles and larger arterioles as irregularly periodic dilatations that are slower and more regular than the diameter changes seen in metarterioles and precapillary sphincters. When metarterioles were exhibiting vasomotion, they usually showed a decrease in diameter of about one-third, but were even seen to reduce the diameter by one-half or more. Other observations were that when a tissue was hyperemic, the dilator phase was most prominent, the constrictor phase dominating in ischemic tissue. No synchrony in vasomotion of neighboring arterioles was seen. Vasomotion was seen to continue in a metarteriole in the absence of blood flow through it. Also, diminished blood flow was followed by an increased dilator phase, while increased blood flow apparently brought on an intensified constrictor phase. Vasomotion was affected by local environmental conditions (irritation of the tissue caused vasomotion to disappear). Vasomotion also stopped when the animal was deeply anesthetized.

The recurrent vasomotion in metarterioles was considered by Chambers and Zweifach to be the factor which controls the rate of flow through the central vessels of a capillary bed while the vasomotion of precapillary sphincters controlled the flow through the true capillaries.

An extensive discussion of vasomotion by Nicoll & Webb (88) in 1946 described various types of caliber changes seen in both arterial and venous vessels. They suggested that the word vasomotion should be preceded by a suitable adjective to indicate a specific kind of change in vessel diameter, e.g., if the caliber change is brought about by contraction or relaxation of the vascular musculature, reference should be made to active vasomotion. If, on the other hand, caliber changes are produced by internal or external alterations of pressure not due to the activity of vascular musculature, reference should be made to passive vasomotion. Active vasomotion was further classified into three groups. "Tonic active vasomotion" was the term used to describe the maintained contraction of arteries, considered to be a tonus response. Superimposed on tone was the rapid contraction and relaxation of vessels that occur in response to nerve impulses. This was called irregular active vasomotion. The third type of movement was called rhythmical active vasomotion and referred to a regular alternation of contraction and relaxation of the vascular smooth muscle.

An analysis of the various types of active vasomotion, as given by Nicoll & Webb (88), follows. That arteries and arterioles possess tone, or are in a continuous state of active contraction, can best be demonstrated by noting the marked increase in their diameter that follows denervation. The diameters of arterial vessels in a denervated area have been shown to increase 27 to 29 per cent following nerve section (134). Nicoll and Webb state that the outstanding characteristics of tonic active vasomotion are its constancy and sluggishness, and suggest it may function to correlate blood vessel volume and blood fluid volume.

Irregular active vasomotion is characterized by rapid changes in the caliber of arteries and arterioles. The changes vary as to their magnitude and the length of time they endure. Such caliber changes are the direct result of impulses from the vasomotor nerves, controlled by the vasomotor center. Nerve section obliterates this type of activity. Nicoll and Webb are of the opinion that the function of irregular active vasomotion is to modify peripheral resistance and also to regulate the pressure gradient in the capillaries.

Rhythmical active vasomotion is the third type of activity seen in vascular beds. It has been observed in arteries, arterioles, precapillary sphincters, and veins. This regular alternation of contraction and relaxation of vascular smooth muscle cells has been shown to continue after denervation (129). It becomes more marked in the most peripheral vessel, the best example of it on the arterial side being at the level of the precapillary sphincters. It is the predominant type of activity shown by veins. In general, the more normal conditions are, the more outstanding is the rhythmical active vasomotion.

Nicoll & Webb (88) offer several reasons to give support to the hypothesis that this rhythmical activity is the result of an inherent property of smooth muscle cells rather than the response of vascular muscle to a rhythmical discharge from the vasomotor center or from humoral influences or physical conditions. The reasons are these: *a*) Terminal arterioles, precapillary sphincters, and veins exhibit rhythmical active vasomotion after denervation. *b*) This type of vasomotion is most highly developed in the venous muscular coat and precapillary sphincters, neither of which appears to be under direct control of vasomotor nerves. *c*) Adjacent vessels vary independently in the rate and magnitude of their rhythmical activity.

Rhythmical active vasomotion in veins is frequently powerful, reducing the vascular lumen to one-third or one-fourth of its resting diameter at the peak of contraction. The rate at which the contractions and relaxations occur is usually much faster than that observed in arterial vessels.

In later reports, Chambers & Zweifach (19, 22) discussed vasomotion and its relation to fluid exchange across the capillary wall. The term "vasomotion" was still used only in reference to spontaneous contraction and relaxation of the metarteriole and its branches. Vasomotion in the precapillary offshoots was said to produce alternate periods of varying hydrostatic pressure, thus greatly influencing fluid exchange in the capillary bed. When vasomotion was reduced or absent, blood pressure in the arterioles was spread through the numerous capillaries of the bed resulting in a slower flow through the capillaries and a subsequent accumulation of fluid in the collecting venules. Such a situation would create a sufficient back pressure to favor outward filtration. When vasomotion was active, blood flow went primarily through the arteriovenous pathways, bypassing the capillary vessels and producing a rapid flow in collecting venules. This bypassing of capillaries would favor drainage from the capillary network, a condition which would

increase inward filtration. In summarizing the significance of vasomotion in fluid exchange in the capillary bed, they state that the delicate vasomotor adjustments, which vary the surface area over which hydrostatic pressure may cause outward filtration, play a greater role than the differences between hydrostatic and colloidal pressure. Osmotic uptake, which is responsible for inward filtration, is dependent upon and reinforced by adequate venous outflow, a factor influenced by vasomotion.

Webb & Nicoll (130) refer to rhythmical active vasomotion as being the outstanding activity in the entire minute vascular bed and regard it as the principal factor of a local nature that regulates blood flow, and probably pressure, in the capillaries. All types of anesthesia reduce or abolish active vasomotion of the smaller vessels, and the authors suggest that this may be the reason why such activity is overlooked in many vascular studies. Active vasomotion is greatly reduced in conditions in which vascular flow is sluggish or irregular, or when the arterial pressure is low. Active vasomotion in arterioles can be augmented by sudden increases in intra-arteriolar pressure.

Active vasomotion was further discussed by Nicoll & Webb (89) in a paper in which investigations to determine the effect of environmental changes on active vasomotion were described. Arteries and the largest arterioles were said to show two types of active vasomotion, one being a slowly developing diameter change dependent on tonus and the other, a rapid diameter change dependent on the response of vascular muscle to nerve excitation. The smaller arcuate and terminal arterioles showed active vasomotion independent of nerve connection, and no classification of this activity into tonus changes or contractile responses was possible. However, two different types of muscular activity were seen in these small vessels, one being peristaltic waves sweeping along the terminal arterioles and the other being localized contraction of the precapillary sphincters.

The effect that active vasomotion has on blood flow through capillary beds depends on both its intensity and its duration. When constriction is not great enough to close the lumen completely, plasma and platelets continue to flow through the capillary vessels while the cellular elements are held back. This is referred to as "plasma skinning." When contraction of the vascular muscle is great enough to occlude the lumen, blood flow into the capillary nets is necessarily curtailed. The occlusion is normally temporary, resulting in intermittent flow through the capillary nets.

Veins and venules in the bat wing with smooth

muscle as a component of their walls exhibit marked active vasomotion. Nicoll and Webb describe the contraction as sharp, and one that sweeps along the vein as a peristaltic wave in a central direction. Each wave of contraction seems to originate at a distal valve and die out at the next valve central to it. Since the majority of valves are located at the confluence of tributaries, valve action and blood flow may seem unrelated due to asynchronous waves in two segments which are separated by their valves.

Two major tributaries which form a vessel may contract alternately. One tributary may empty into a segment ahead while the other tributary is relaxed. Irregular flow results when the frequency of contraction of the two tributaries is not coordinated. Single tributaries empty into a segment of the central vessel during its period of relaxation.

Nicoll and Webb adopt the concept that vascular smooth muscle cells possess an inherent ability to change their tonus or exhibit sudden contraction in response to changes in their immediate environment. In order to determine what environmental changes affect vascular smooth muscle, they observed changes in vasomotion in response to nerve stimulation, various gas mixtures, and temperature changes. They found that arteries and large arterioles responded to nerve stimulation with intense constriction. The smaller vessels, arcuate and terminal arterioles, precapillary sphincters, veins, and venules never showed initiation or modification of active vasomotion as a direct response to central impulses (129). Changing the local environment by flow of constant current between a single fluid electrode on the wing surface and an indifferent electrode produced alternate areas of marked constriction and dilatation on arteries and arterioles. Reversal of the current caused previously constricted areas to dilate and previously dilated areas to constrict. Nicoll & Webb (89) believe that this observation should be taken into account when interpreting responses to direct excitation of nerves with microelectrodes. Inhalation of carbon dioxide in a specific concentration proved to be a powerful stimulus of the contractile phase of active vasomotion. Variations in temperature showed the frequency of active vasomotion to vary directly with the temperature.

Changes in internal pressure of vessels have marked effects on vasomotion. Slow changes in pressure caused a vessel to adjust its tone gradually. Sudden increases in pressure, however, first caused a vessel to be distended mechanically and then to contract with great intensity. The contraction then spread along the

vessel as a peristaltic wave. Nicoll and Webb suggest that rhythmical variations in small arterial vessels may originate from sudden internal pressure changes at their origins from parent vessels.

Spontaneous changes in vascular tone, resulting from a rise or fall in internal pressure, were demonstrated. After blood flow to an area had been stopped by occlusion of a small supplying artery and was then allowed to resume, the vessels were first distended as they filled and then were seen to contract as a response, presumably, to the distention. Thus, blood was forced along to the next branches. Another example of adjustment of tone to a change in internal pressure is seen following denervation. The resulting dilatation of the main arteries probably raises internal pressure in the arterioles and increases their tone, sometimes reducing the flow through the arterioles to the capillary beds due to the reduction in lumen of the arterioles.

Nicoll and Webb express the opinion that the ultimate result of active vasomotion in terminal arterioles is to establish flow through capillary beds, the muscle cells of the terminal arterioles being the principal targets of changes in the local environment.

Active vasomotion in venules and veins may represent the adaptation of an inherent property of vascular smooth muscle to aid venous return. Nicoll and Webb suggest that this activity may be more widespread in vascular systems than is currently recognized. It may be more prominent in the veins of the bat wing than in small veins in other mammals due to the structure of the wing. Pressure within the veins seems to be the principal stimulus for the action.

Experimental evidence in confirmation of this proposal appears in the investigations by Wiedeman (135), in which veins in the bat wing were observed during elevations in venous pressure. Both diverting excess blood into a vein by ligating other venous pathways and infusing dextran to increase total volume caused a significant increase in cycles of venous vasomotion. Similar results were obtained when venous pressure was elevated by direct infusion with saline (136).

Although venous vasomotion is most prominent in the bat wing and shows a definite rhythmicity (fig. 24), spontaneous changes in pressure which are unrelated to arterial pressure or respiration have been demonstrated in small veins in hind legs of dogs (59, 137)

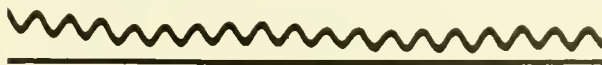


FIG. 24. Rhythmical variations in the pressure in a vein resulting from alternate contraction and relaxation.

(see fig. 25). Such changes have also been recorded in rabbit ear veins (unpublished data). (See fig. 26.) Recently, spontaneous changes in venous tone were recorded from the arm veins of man (16). Folkow has long supported the concept that rhythmic changes in tone of vascular smooth muscle is due to myogenic automaticity (42, 43, 45, 46). He points out (45) that because the rhythmical reactions seem to be completely unsynchronized, even in closely adjacent smooth muscle cells, it is improbable that they should be due to activity in a local syncytial nerve cell plexus in the vascular wall, as suggested by others (85). He is of the opinion (43) that intravascular pressure in a purely mechanical way to some degree will add "excitatory drive" to myogenic activity as proposed by Bayliss (10) and confirmed in Folkow's laboratory (42). Further confirmation appears in recent studies of forearm blood flow by Blair *et al.* (12).

At the present time then, in concurrence with Lutz & Fulton (81), the term "vasomotion" should refer to any active change in the diameter of a blood

vessel. It may be seen in one form or another where vascular smooth muscle exists, such as in arteries, arterioles, terminal arterioles, precapillary sphincters, venules, and veins. Any definite conclusions now as to the actual mechanism or mechanisms which initiate or control this vascular activity would be premature insofar as both direct and indirect evidence indicate that vasomotion in its various forms may be activated or modified through the central nervous system, reflexly or automatically, through myogenic automaticity, or through local metabolic factors.

This activity in venous vessels, especially if primarily dependent on myogenic automaticity excited by increased intravascular pressure, could serve as an effective aid to venous return from postcapillary vessels. On the arterial side it could serve as the regulator of blood flow through capillary nets as well as a protective mechanism whereby capillary vessels could not be subjected to sudden or prolonged increases in pressure which might rupture their thin walls.

FIG. 25. Spontaneous pressure waves in a small vein in the hindleg of the dog. [From Wiedeman (137).]

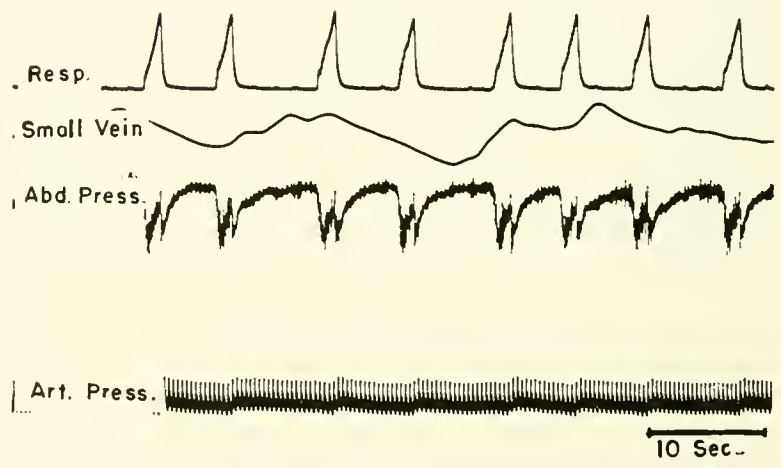
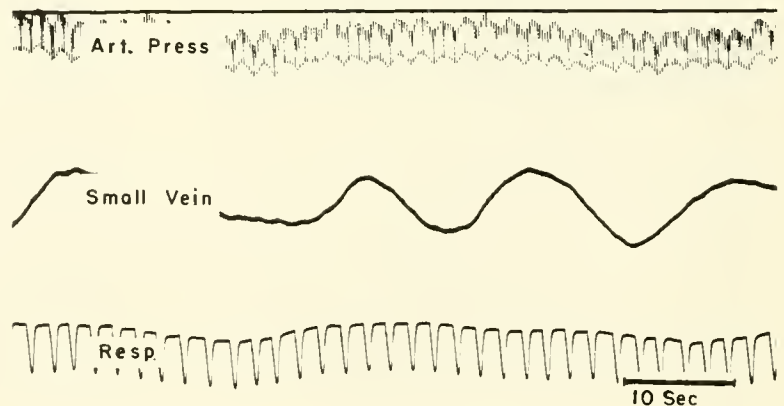


FIG. 26. Spontaneous pressure variations in a small vein of the rabbit ear.



SUMMARY

It is apparent, from the foregoing descriptions of structural organization of microcirculatory beds and regulation of the flow of blood through them, that the investigations have revealed more similarities than dissimilarities. Minor differences among patterns seem to be associated with the structural organization of the tissue in which the vessels lie, but the basic patterns remain the same.

Although presentation of an anatomical pattern that would be "typical" for terminal vascular beds would be likely to meet some resistance, it does seem necessary to agree on such features as arcuate or arcade connections, gradual divestment of spiral smooth

muscle cells along terminal arterioles to form capillaries, absence of direct association and control of capillaries through nerves, and similarity of the courses taken by small arteries and small veins. Also, certain functional activities which regulate blood flow and blood pressure through these beds must be considered as universal, these being spontaneous vasoconstriction and relaxation of arterioles, reversal of flow paths, alternation of routes of blood flow from arterial to venous vessels, and variations in the filling of capillary networks depending on local conditions. Future investigations may permit generalizations concerning the angles of branching in the arterial system and spontaneous vasomotion in the venous system.

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Resistance (conductance) and capacitance phenomena in terminal vascular beds¹

HAROLD D. GREEN

CARLOS E. RAPELA

MARGARET C. CONRAD²

*Department of Physiology and Pharmacology, Bowman Gray
School of Medicine, Wake Forest College, Winston-Salem, North Carolina*

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Interpretation of Vascular Behavior from Measurements of Flow, Pressure, and Vascular Volume

SINCE MOST VASCULAR BEDS do not permit direct microscopic study, indirect methods have to be used to evaluate them. In this chapter, the behavior of vascular beds is deduced from recordings of the rate of blood flow, the accompanying small vessel pressures, and the changes in vascular volume that occur as the result of varying the artery to vein pressure difference across the bed and as a result of other intrinsic and extrinsic influences.

Using the above measurements, the role of the terminal vascular beds is analyzed in terms of the behavior of those segments which determine the resistance to flow through the bed, i.e., the resistance vessels, and those segments which are related to the volume of blood contained in a terminal bed at any moment, i.e., the capacitance vessels. These functions of the terminal vascular beds are shown to be influenced by such physical factors as arterial perfusion pressure, presence of communication with collateral vascular beds, viscosity of the blood, extravascular pressure, venous pressure, by local autoregulation, and by extrinsic factors such as vasoactive agents and the autonomic nerves.

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² Formerly trainee, Cardiovascular Graduate Training Program (HTS-5392) National Heart Institute, United States Public Health Service; currently Fellow of the American Heart Association.

RESISTANCE VESSELS

Pressure-Flow Relations in Vascular Beds

METHODS. Pressure-flow relations in vascular beds have been studied by two principal methods. In one, the bed was perfused by a constant flow pump at various flow rates while the artery to vein pressure differences were recorded. More usually inflow or outflow from the vascular bed was recorded while the perfusion pressure was varied by using a constant pressure pump or by varying the degree of compression of the artery supplying the vascular bed. In most cases, the arterial and venous pressures were recorded together with the flow. Varying perfusion pressure by altering the degree of compression of the supplying artery has the advantage of providing a more nearly physiological situation with a minimum of complicating equipment, but does not allow exploration of the pressure-flow relationships above the animal's existing mean arterial pressure. Flow has been measured by orifice meters, rotameters,

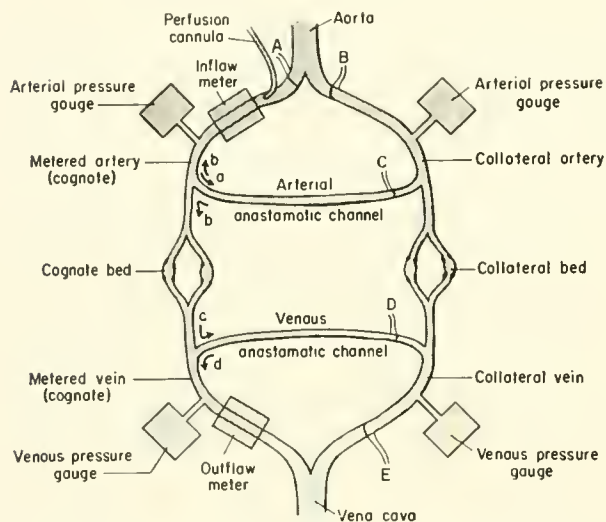


FIG. 1. Diagram of collateral communications between a metered (cognate) capillary bed and collateral bed. *Inflow meter*—meter used to measure flow through the metered or cognate bed; *outflow meter*—meter used to measure the outflow from the metered or cognate bed; *anastomotic channels*—communications between cognate bed and collateral bed on the arterial and venous sides, respectively, of the metered or cognate bed. *A*—clamp used to occlude the inflow to the metered bed when perfusing it with fluid at various pressures; *B*—position where clamp might be placed to occlude the arterial supply to a collateral bed; *C* and *D*—positions where clamps must be placed in order to occlude the communications between cognate and collateral beds; *E*—point of occlusion to prevent outflow from a collateral bed. [Modified from Green *et al.* (41).]

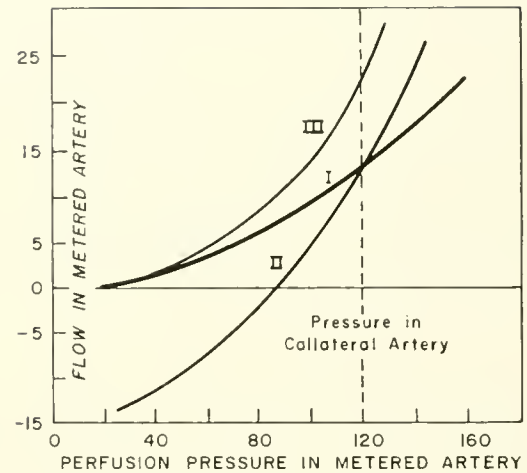


FIG. 2. Relationship between perfusion pressure and arterial inflow. *I*—curve representing the direct relationship between arterial pressure and flow through the cognate bed when clamps were applied to the arterial anastomotic channels as at point *C* in fig. 1. *II*—artificial curve obtained if clamp *C* remains open when the arterial pressure supply to the cognate bed is varied. Note that at perfusion pressures higher than that existing in the collateral artery, the metered flow is greater than the flow through the cognate bed, and at pressures a little below that in the collateral artery, the inflow is less than that through the cognate bed while at some lower perfusion pressure backflow is recorded. *III*—artificial curve obtained if clamps are applied to the arterial supply to the collateral bed as at point *B* in fig. 1. Note that while no backflow is obtained, the metered inflow is greater than the flow through the cognate bed at all levels of pressure, and the magnitude of the error increases with the perfusion pressure. [Modified from Green *et al.* (41).]

electromagnetic flowmeters, drop recorders, and Gaddum-type ordinate recorders (20, 27–29, 46).

In studying pressure-flow relationships in intact vascular beds, it is necessary that all anastomotic communications with collateral vascular beds be occluded. If they are not, then, during measurement of inflow at perfusion pressures above the animal's mean arterial pressure, part of the perfusion fluid will leak across the anastomotic channels from the cognate into collateral vascular beds (fig. 1-a), giving an inflow which is higher than the true flow through the cognate bed (fig. 2-II). Similarly, at perfusion pressures below the animal's mean arterial pressure, blood will leak across the communicating channels from the animal's collateral arteries to the metered (cognate) vascular bed (fig. 1-b); as a result the metered inflow will be less than the actual flow through the cognate bed. At some lower pressure inflow in the metered artery will cease and, at still lower pressures, backflow from the artery will be recorded, thus giving an entirely false picture of the

behavior of the cognate vascular bed (41). Analysis of the rate of backflow may be useful, however, as a measure of the effectiveness of existing communications between cognate and collateral arteries.

Errors analogous to those on the arterial side may occur when recording venous outflow, due to the presence of postcapillary communications with veins draining collateral vascular beds (fig. 1-c, d).

PASSIVE CURVILINEAR RELATIONSHIP OF PRESSURE-FLOW PLOTS. The simplest relationships between pressure and flow occur in vascular beds which do not show autoregulation such as skin or "nonreactive" hind limbs (46, 88, 115) or the pulmonary vascular bed (78). All such curves are curvilinear with the convexity toward the pressure axis (fig. 3). In such studies changes of vasomotor tone have occurred spontaneously (46) or have been induced by infusion of epinephrine (88). With increase in vasomotor tone the curves rotate toward the pressure axis so that for any given level of pressure, flow is less (fig. 3). In all such experiments, using blood as the perfusate, the curves approach the zero flow axis asymptotically. A "critical closing pressure," such as was described by

Burton (6) and others (10, 37) was not noted in the above studies (see also 32, 35, 64). Curves of this type may be said to exhibit a "passive" relationship between pressure and flow.

MATHEMATICAL RELATIONSHIPS. When the data from the above experiments are plotted on log-log paper, approximately straight lines with varying foci and slopes are obtained (fig. 3). It appears, therefore, that the mathematical relationship between flow and pressure is a power function

$$F = c \times P^n$$

where F = flow in ml per min, c is a constant, P = arteriovenous pressure difference in mm Hg, and n is an exponent having a value between 1 and 3 (46). The lowest value of n and the highest value of c were found at "low vasomotor tone" (fig. 4, point A) and vice versa (fig. 4, point C). Levy & Share (74) have confirmed these findings and demonstrated that with maximal dilation induced by a 10-min period of ischemia and subsequent perfusion with hypoxic blood, the value of n is 1.0. The relationship of c to n

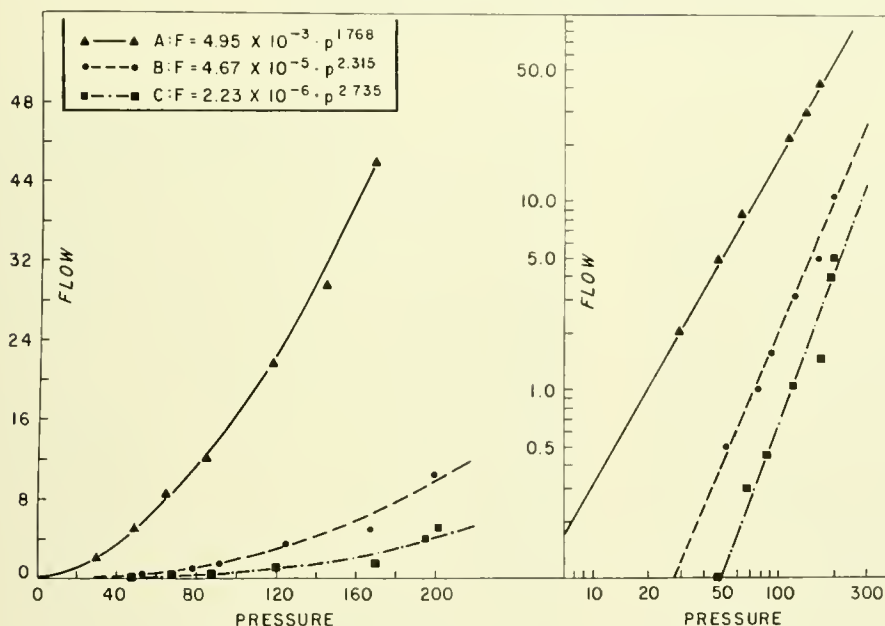


FIG. 3. Plots of the arteriovenous difference pressure vs. the blood flow in a cutaneous (saphenous) bed at three levels of spontaneous "vasomotor tone." *Left half*, plotted linearly; *right half*, plotted on log-log paper. *Triangles* represent the lowest level of vasomotor tone; *circles* represent an intermediate level and *squares*, the highest level of vasomotor tone. The figures in the upper left-hand corner of the graph represent the parameters for the straight lines reproduced in the log-log plot and for the curvilinear lines reproduced in the linear plot. Flow—ml/min; pressure—mm Hg. [Modified after Green *et al.* (46).]

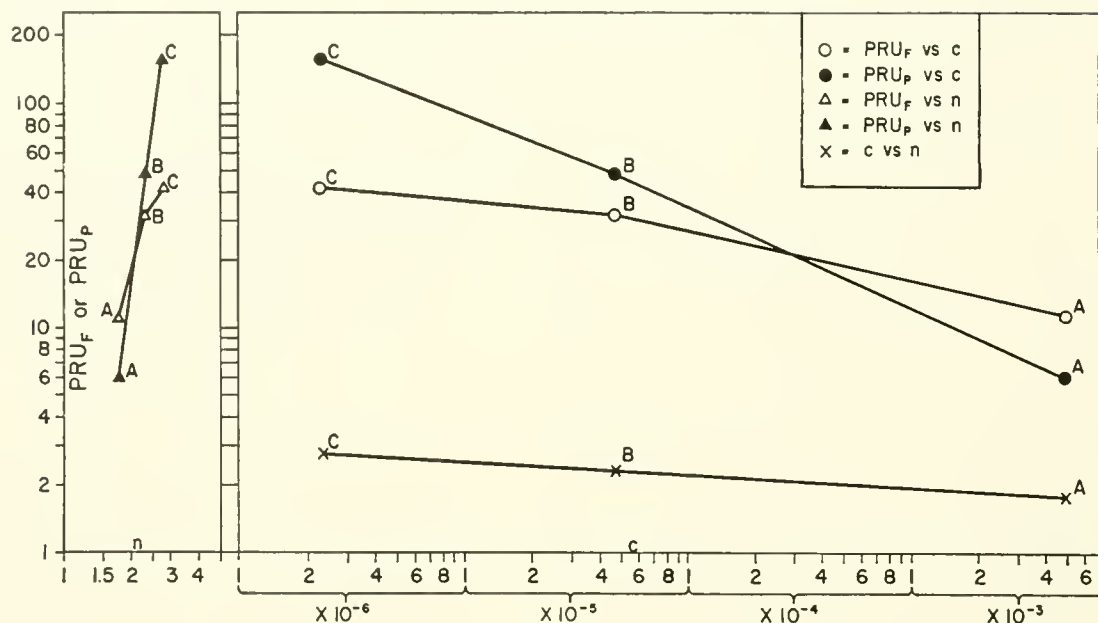


FIG. 4. Log-log plots of the interrelations of the parameters from fig. 3. Open circles—plot of the relationship of the resistance at a flow of 5 ml/min to the constant c ; solid circles—plots of the relationship of the resistance at a perfusion of 100 mm Hg to the constant c ; open triangles—plots of the resistance at a flow of 5 ml/min to the exponent n ; solid triangles—plots of the relationship of the resistance at a pressure of 100 mm Hg to the exponent n ; x —plot of the relationship of the constant c to the exponent n ; points labeled A, B, and C refer to curves A, B, and C, respectively, in fig. 3. Ordinate scale applies to resistance at a flow of 5 ml/min (PRU_F), to resistance at a perfusion pressure of 100 mm Hg (PRU_P), and to n . Abscissal scales apply to n (left graph) and to the constant c (right graph). See Table 1 for further identification of symbols.

in the above experiments (46) was also approximately linear in a log-log plot (fig. 4).

There are at least two possible explanations for a value of n greater than 1. *a*) The apparent viscosity of whole blood decreases as the pressure difference across a length of rigid capillary tubing 0.3 mm or less in diameter is increased, i.e., as flow increases (40); this is due probably to the red cells being clumped progressively closer together as a solid core in the middle of the tube as the rate of flow increases, leaving a sleeve of plasma adjacent to the intima of the blood vessel and thus reducing viscous drag. *b*) Other factors being constant, flow through a conduit is proportional to the fourth power of the diameter. If, with increasing internal pressure, a slight but progressive increase in the diameter of the resistance vessels occurs, then flow through vascular beds containing such distensible structure will increase in proportion to some power of P greater than 1 [Green *et al.* (46); Folkow (27–29, 32)]. From the data in figure 4 it appears that these effects become augmented with increase in “tone” of the resistance vessels. Computations, based on data compiled by Burton (7), indicate that an increase of internal

pressure from 0 to 102 mm Hg in an arteriole might increase the cross-sectional area sufficiently that the relative conductance would be 146 per cent of that at zero pressure, i.e., at the unstretched diameter (fig. 5). However, Baez & Lamport (2) report that arterioles of 34 to 42 μ diameter showed essentially no change in diameter under considerable pressure variation. They did note selective closing of pre-capillary sphincters at positive pressures.

The relationship of resistance to flow, PRU (peripheral resistance unit = P/F = mm Hg (ml/min)), to either flow or A-V pressure difference was also a power function in the above studies; for each level of tone the resistance to flow varied inversely with either flow or perfusion pressure (table 1). Since both the constant and the exponent varied as vasomotor tone changed, the relationship of resistance at one level of tone to that at another (B/A; C/A in table 1) was also a power function of either flow or pressure; this ratio, which was inversely related to pressure and flow, can be expressed as a number if the same pressure (i.e., 100 mm Hg = PRU_{P100}) or flow (i.e., 5 ml/min = PRU_{F5}) is used for each curve (table 1).

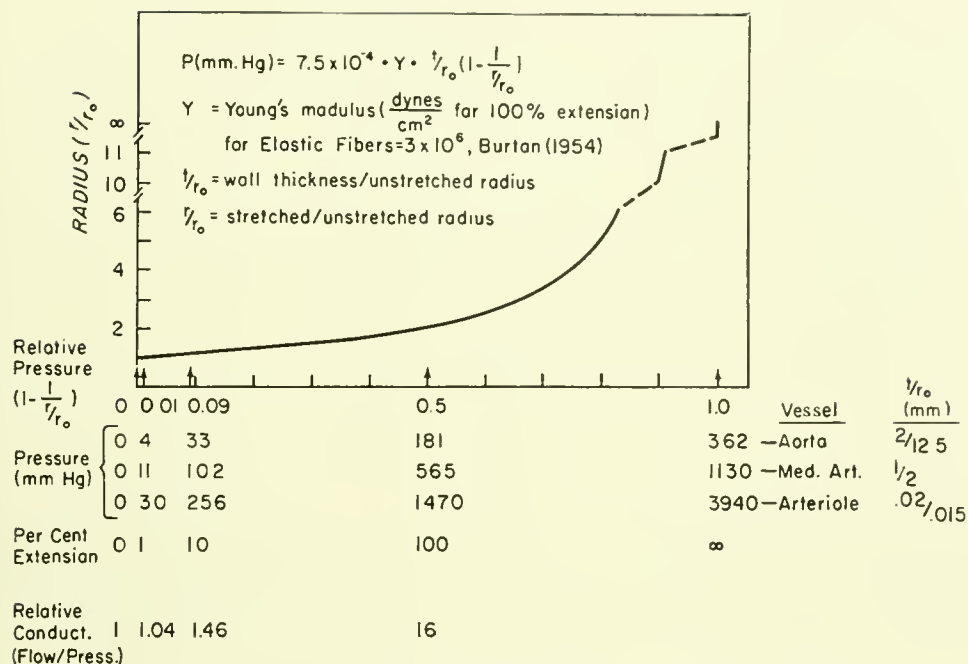


FIG. 5. Relationship of internal pressure to radius in elastic tubes. Radius is expressed as ratio of the radius at any pressure to the unstretched radius (r/r_o). Pressure is plotted over the range from zero to 1, 1 representing that pressure at which the vessel extends indefinitely, and zero the pressure at which the vessel is unstretched. Corresponding values of actual pressure, opposite the bracket, are given in mm Hg; below this is given the per cent extension of the vessel at each of the levels of relative pressure, and below that is given the conductance which the vessel would have relative to that in its unstretched state. Conductance is expressed as the ratio of flow to pressure drop along unit length of the vessel. These plots are calculated from data in Burton (7).

It is of interest that c' vs. n' and c'' vs. n'' (table 1) both plotted as straight lines on log-log paper, as did c vs. n in figure 4. It is of interest also that the lines on the log-log plot in figure 3 approach each other at high pressures and flows. As a result, if the data could be extrapolated to such values, a point would be found at which the resistance in state B would equal that in A (i.e., $P = 5,000$, $F = 16,000$) and another point at which the resistance in state C would equal that in A (i.e., $P = 2,950$, $F = 5,400$). In a log-log plot these two points are so close together that a common point of intersection could be assumed for all three lines—A, B, and C. This suggests that a rise of perfusion pressure acts to overcome the constrictor tone, and that this effect is proportionally greater the higher the vasomotor tone.

From the above data it appears that the most satisfactory method for defining "vasomotor tone" in passive vascular beds is by means of a pressure-flow plot, or by means of the equation for such plot. The best quantitative expression for the comparison of vasomotor tone at one moment with that at another is to determine the plot of the pressure-flow relationship during a control phase of vasomotor tone and to

compare this with a similar plot obtained in the experimental period (see fig. 3 and table 1, columns B/A, C/A, lines II and III). Often this mode of expression is impractical because of the difficulty in maintaining vasomotor tone constant, particularly in the experimental period. A more practical compromise for expressing change of vasomotor tone may be to determine the pressure-flow relationship over a suitable range of pressures and/or flows during the control period and to compare isolated experimental observations of pressure and flow with this control curve (see figs. 21 and 22 and table 1, columns B/A, C/A, lines IV, V).

From an inspection of figures 3 and 4 and table 1, it appears that comparison of the experimental perfusion pressure with that required in the control period to induce the same rate of flow (table 1, lines III and V) may provide a ratio which approximates the apparent separation of the lines more nearly than does the ratio of pressures at constant flow (table 1, lines II and IV). This would provide merit in perfusing passive (nonautoregulating) vascular beds at a constant rate of flow while recording the

TABLE 1. *Mathematical Relationships Between Resistance and Pressure and Between Resistance and Flow*

| | | A | B | C | B/A | C/A |
|-----|-------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|
| I | $F = c \times P^n$ | $4.95 \times 10^{-3} \cdot P^{1.768}$ | $4.67 \times 10^{-5} \cdot P^{2.315}$ | $2.23 \times 10^{-6} \cdot P^{2.735}$ | $\frac{P^{0.547}}{1.05 \times 10^2}$ | $\frac{P^{0.967}}{2.22 \times 10^3}$ |
| II | $PRU_P = \frac{c'}{P^{n'}}$ | $\frac{2.02 \times 10^2}{P^{0.768}}$ | $\frac{2.14 \times 10^4}{P^{1.315}}$ | $\frac{4.40 \times 10^5}{P^{1.735}}$ | $\frac{1.05 \times 10^2}{P^{0.547}}$ | $\frac{2.22 \times 10^3}{P^{0.967}}$ |
| III | $PRU_F = \frac{c''}{F^{n''}}$ | $\frac{20.3}{F^{0.434}}$ | $\frac{74}{F^{0.668}}$ | $\frac{116}{F^{0.635}}$ | $\frac{3.65}{F^{0.134}}$ | $\frac{5.72}{F^{0.201}}$ |
| IV | $PRU_{P_{100}}$ | 5.93 | 50.3 | 152 | 8.49 | 25.6 |
| V | PRU_{F_5} | 10.1 | 29.7 | 41.8 | 2.9 | 4.14 |

The columns correspond to the curves: A = solid triangles; B = solid circles, and C = solid squares in fig. 3. PRU_P = resistance in mm Hg/(cc/min) expressed as a function of the arteriovenous difference in pressure in mm Hg; PRU_F = resistance expressed as a function of the rate of flow; $PRU_{P_{100}}$ = resistance computed at an arteriovenous pressure difference of 100 mm Hg; PRU_{F_5} = resistance calculated at a flow of 5 cc/min; B/A and C/A = ratios of values in columns B and C, respectively, to those in column A. *Note*—columns B/A and C/A: for lines II and IV these values are also reciprocal ratios of flow at constant arteriovenous pressure difference and for lines III and V they are also direct ratios of arteriovenous difference of pressure at constant rate of flow.

$$F = c \times P^n$$

$$PRU_P = \frac{P}{F} = \frac{P}{c \cdot P^n} = \frac{c^{-1}}{P^{n-1}} = \frac{c'}{P^{n'}}$$

$$PRU_F = \frac{P}{F} = \frac{F^{1/n}}{c^{1/n} \cdot F} = \frac{c^{-1/n}}{F^{1-1/n}} = \frac{c''}{F^{n''}}$$

The data in this table were computed from results reported by Green *et al.* (46).

arteriovenous difference of pressure during experimentally induced changes of vasomotor tone.

On the other hand the convergence of the pressure-flow plots at high pressures, discussed above, suggests a secondary influence of change of perfusion pressure on vascular distensibility and measured resistance. On this basis there is merit in using a constant perfusion pressure and allowing the flow to vary with experimentally induced changes of vasomotor tone rather than keeping the flow constant and allowing the perfusion pressure to be the dependent variable. At present we cannot find sufficient grounds for a decision between the two methods of perfusion when studying "passive" vascular beds.

In those vascular beds which show autoregulation (p. 948) anything which induces a change of flow, i.e., alteration of perfusion pressure, tends to be countered by an active change of vasomotor tone which will tend to maintain flow constant. In this type of bed it is particularly desirable to have data on the control steady-state pressure and flow relationships in order to make adequate quantitative comparisons with experimental data.

Effects of Viscosity on Pressure-Flow Relationships

The viscosity of blood relative to that of water increases nonlinearly with red cell concentration,

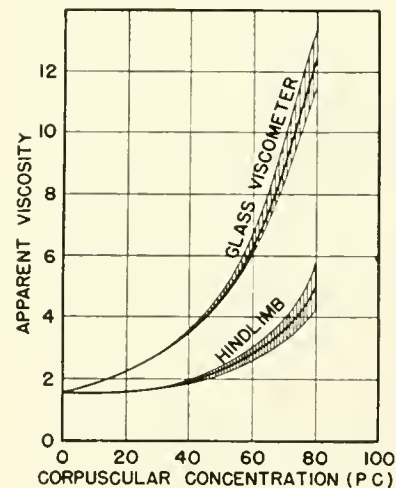


FIG. 6. Mean and probable error of the apparent viscosity of blood relative to saline in a glass viscometer and in the hind limb of a dog at different corpuscular concentration. [Redrawn after Whittaker & Winton (115).]

varying from around 2 with pure plasma to around 5 at high hematocrit readings when measured in a low velocity viscosimeter (fig. 6). Lower relative viscosities are obtained with high velocity viscosimeters and still lower relative viscosities are noted in perfused organs. The relative viscosity in the latter two systems decreases as the pressure difference and flow rate are raised. Most of the viscosity of normal blood is due to the suspended red cells, but the effect of the cells is slight until the hematocrit begins to exceed 30 per cent (40, 74, 115); however, the plasma proteins, particularly the globulins, contribute significantly (112). In terms of effective oxygen delivery to the tissues, a hematocrit of around 45 appears to represent the best compromise between viscosity and O_2 carrying capacity (50).

Effects of Extravascular Pressure on Pressure-Flow Relationships

In most vascular beds extravascular pressure exerts little effect. However, in muscle vascular beds, a marked increase in resistance to flow occurs with contraction. This is exemplified best in the myocardium in which during systole a rise in resistance

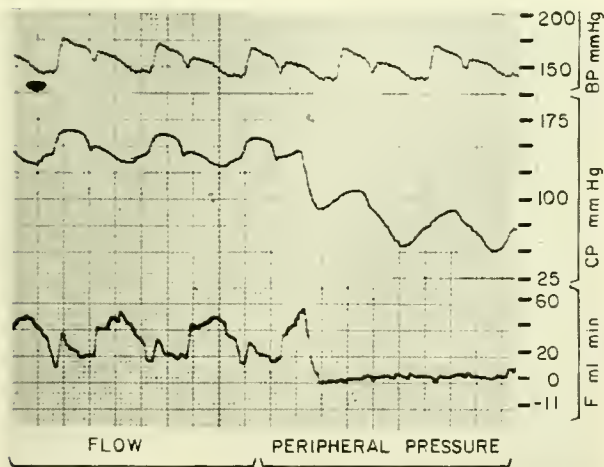


FIG. 7. Records of systemic arterial pressure (BP), and lateral pressure (CP) and moment-to-moment flow (F) in the descending ramus of the left coronary artery during the period labeled "flow." During the period labeled "peripheral pressure" flow was interrupted by occlusion of the coronary artery inflow proximal to the site of pressure measurement so that the gauge recorded "peripheral coronary artery pressure." Note that the latter pressure begins to rise during the phase of isometric contraction that precedes the rise of systemic arterial pressure, and that the peripheral coronary pressure begins to fall with the onset of protodiastole, just before the incisura in the systemic arterial pressure. [Reproduced in modified form from Denison & Green (19).]

occurs which closely parallels intraventricular pressure in magnitude and duration, as shown in figure 7 (19, 43).

Coles & Gough (10) applied external pressure to a cup applied to a digit while observing the capillaries with a microscope. They noted that arrest of capillary flow occurred consistently at cup pressures of 32 to 60 mm Hg in subjects with mean brachial artery pressures of 80 to 120 mm Hg obtained with the sphygmomanometer. They spoke of the pressure at which flow ceased as the critical closing pressure and reported that it rose with the arterial pressure in hypertensives and fell with digital vasodilation induced by body warming. The use of the term "critical closing pressure" in this sense seems to us to be ambiguous. Quite possibly, in their experiments the pressure decreased progressively from the brachial artery to the small digital arteries. If this were the case the vessels in the digits may have collapsed when the extravascular pressure just exceeded the intravascular pressure. However, since the true intraluminal pressure of the vessels which close was unknown, the role of the elastic forces producing critical closure (see Burton, Chapter 6, vol. 1, sect. 2, of this *Handbook*) as against the role of simple mechanical collapse can hardly be differentiated. This makes it quite difficult to assign a figure for the critical closing pressure if indeed one may use that concept here.

Cerebrospinal fluid pressure may have a tendency to vary directly with cerebral blood flow; however, artificially induced changes of cerebrospinal fluid pressure have little effect on flow unless the pressure is elevated above arterial pressure (76 and unpublished data).

Effects of Alteration of Venous Pressure

When extremities were perfused with varying pressures, while venous pressure was altered simultaneously so as to maintain artery to vein pressure difference constant, flow still varied with the level of the arterial pressure (89). The authors conclude that some vascular structures were dilated as the arterial (and total) pressure throughout the vascular bed rose. In the supine anesthetized dog, inspiration was accompanied by a rise of intra-abdominal pressure and of small vein pressure in the hind leg. Widely opening the abdomen abolished both (113). The small vein pressure effects apparently were transmitted peripherally from the inferior vena cava.

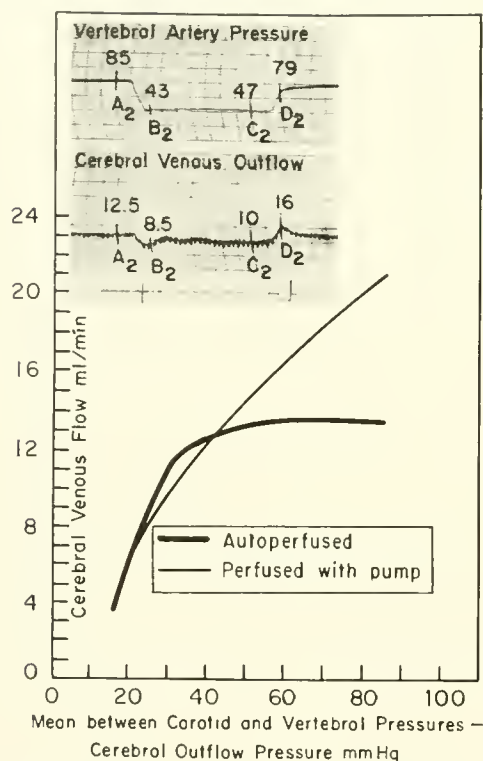


FIG. 8. Autoregulation in the cerebral vascular bed of the dog. *Above:* records representing vertebral arterial pressure in mm Hg and cerebral venous outflow in ml/min. *Below:* heavy solid line, relationship between the cerebral venous outflow and the mean of the carotid and vertebral artery pressures minus the cerebral outflow pressure during autoperfusion of the brain from the carotid arteries. The perfusion pressure was regulated by means of clamps on the carotid arteries. Light solid line, similar relationship but during the perfusion of the carotid arteries with an artificial perfusion system.

Autoregulatory Control of Resistance Vessels

For the purpose of this chapter, we propose that the term autoregulation be defined to include all processes which operate locally in a vascular bed to maintain some factor constant in the face of various externally or internally induced stresses. The factor which is kept constant, i.e., the controlled variable (see below) may be blood flow, or the tissue concentration or tension of some nutrient (O_2 , etc.) or some metabolite (such as CO_2). As proposed here, the term autoregulation would exclude extrinsic mechanisms such as reflexes involving the central nervous system, variation in arterial pressure, or changes in hormone activity.

The activity of autoregulatory mechanisms has been studied by subjecting isolated or semi-isolated organs to stresses such as changes in arterial perfusion pressure or blood gas content, or by altering tissue metabolism while recording the resulting change, or lack of change

in blood flow, venous gas content, or the content of other metabolites.

MODIFICATION OF PASSIVE PRESSURE-FLOW RELATIONSHIP BY AUTOREGULATION. In many vascular beds, the above-mentioned power relationship between perfusion pressure and flow in passive vascular beds is modified by occurrence of autoregulation. The insert in the upper portion of figure 8 shows recordings of blood flow in the brain obtained during autoperfusion (76 and unpublished data). In these studies, carotid artery inflow pressure was lowered abruptly from 84 to 44 mm Hg; after flow stabilized, perfusion pressure was returned to the control level. Immediately upon lowering perfusion pressure, flow dropped from 12.5 to 8.5 ml per min, then rose to a stabilized level of approximately 10 ml per min. Upon restoration of control pressure, flow rose abruptly to 16 ml per min and then stabilized at approximately its original level of 12.5 ml per min. The rise in flow following the initial decline probably was due to vasodilation, and the secondary decline in flow following restoration of the original perfusion pressure probably was due to vasoconstriction. When data from such experiments are plotted they yield a series of curves such as are reproduced in figure 9.

The heavy line in the graph in figure 8 corresponds to the heavy line in figure 9 and is a plot of the stabilized flows at each level of perfusion pressure from 85 to 15 mm Hg. This line is almost horizontal, indicating an almost constant level of stabilized flow over the pressure range of 80 to 35 mm Hg. In view of the observations in figures 3 and 4, this finding can be explained only by assuming some reactive change in the diameter of the resistance vessels so as to compensate for alteration of perfusion pressure (76 and unpublished data). The mechanism responsible for compensation for pressure change has been termed local reaction of the arterial wall, reactive vasodilation, intrinsic regulation, autoregulation and "genuine autoregulation" (3, 27-29, 36, 46, 63, 66, 72, 90, 92, 99, 105, 109, 111).

Observations, similar to those in the brain, were recorded in artificially perfused skeletal muscle vascular beds (fig. 10). At pressures above normal the pressure-flow relationship was curvilinear and similar to that described for skin (fig. 3) and the resistance to flow, after stable flow was established, increased progressively as perfusion pressure was lowered. However, as perfusion pressure dropped below 100 mm Hg the curve began bending more sharply to the left so as to become approximately horizontal to the pressure axis, and the stabilized resistance to flow

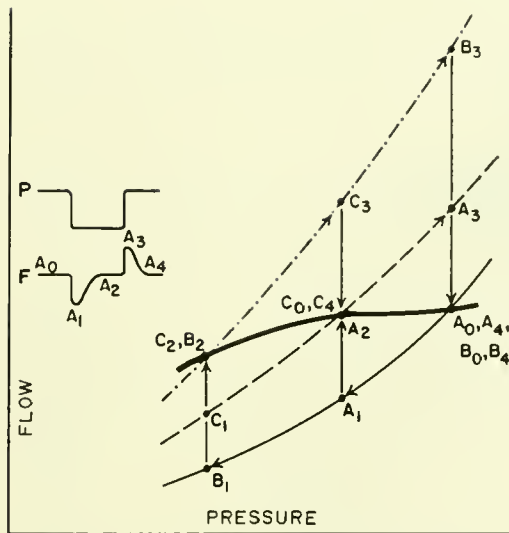


FIG. 9. Sequential flow readings following a series of square wave changes of perfusion pressure in a vascular bed showing autoregulation. The pressure-flow points are numbered successively A_0, A_1, A_2, A_3 , and A_4 for the first square wave change of pressure (on both insert and graph). The points for the second pressure change are numbered similarly B_0-B_4 and for the third, C_0-C_4 . Light solid line represents the pressure-flow relationship which would be found if vasomotor tone remained constant at the level which existed during perfusion at a pressure corresponding to A_0 for a period of time sufficient to establish a steady-state flow at this pressure. Dash-dot line represents the corresponding pressure-flow plot which would be found if the vasomotor tone were to remain constant at a level corresponding to that found when steady-state flow was established at a perfusion pressure corresponding to point B_2 . Dash-dash line represents the pressure-flow plot which would correspond with the steady-state flow established for perfusion pressure A_2 assuming no change in vasomotor tone were to occur with subsequent change of perfusion pressure. These three plots then represent three levels of vasomotor tone. Heavy solid line represents the actual "steady state" pressure-flow relationship after reactive changes have occurred in the vasomotor tone following each change of perfusion pressure; it is the plot characteristic of autoregulation.

decreased with further lowering of perfusion pressure down to about 50 mm Hg. This progressively decreasing resistance tended to maintain flow relatively constant over the range of arterial pressure from 90 down to approximately 50 mm Hg. Below 50 mm Hg arterial pressure, flow dropped rapidly and approached zero at a pressure of 10 to 20 mm Hg.

When the pressures and flows in figure 10A are plotted on log-log graphs (fig. 10B), the portion corresponding to the pressures above 90 mm Hg plots as a straight line with a slope greater than 1; this portion of the curve corresponds to a "passive" relationship between pressure and flow (see above). On the other hand, in the range between 50 and 90 mm Hg the slope is less than 1. In the equation $F = cP^n$, the corresponding values of n are greater than and less than 1, respectively. Values for n of less than 1 are characteristic of autoregulation (28, 29).

ARTIFACTS INDUCED IN AUTOREGULATION STUDIES BY PUMP PERFUSION SCHEMAS. Failure to detect autoregulation in vascular beds has been attributed to occurrence of some alteration in the vascular bed as a result of changes in the blood due to contact with artificial structures or to traumatization of the blood by perfusion pumps (28, 29, 66). This effect is noticeable particularly in the cerebral vascular bed, as shown in figure 8 (76 and unpublished data).

The heavy line in figure 8 represents the stable pressure-flow relationship in a cerebral vascular bed during an initial study when the pressure was regulated by compressing the arteries supplying the brain. The light line gives the stable pressure-flow relationship during a subsequent period when a perfusion pump was inserted in the arterial inflow circuit. With the perfusion pump in operation, flow at all levels of pressure was significantly above that with the brain perfused directly from the heart. Furthermore, the flow did not remain constant but increased regularly

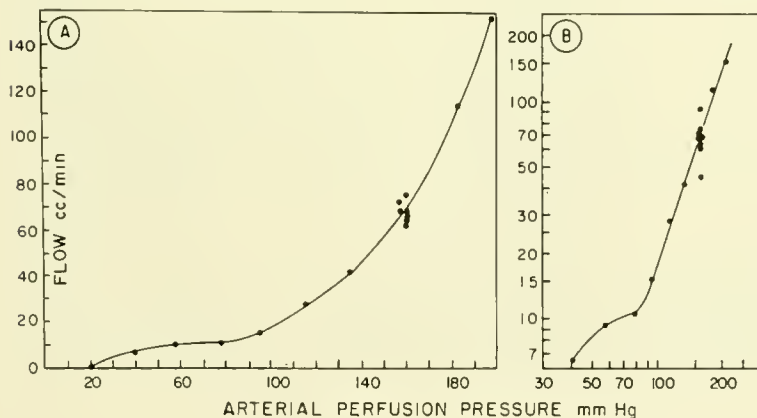


FIG. 10. Plots of the relationship between blood flow in a skeletal muscle vascular bed in the dog and the arterial perfusion pressure (arterial pressure minus venous pressure). A: linear plot; B: log-log plot. Pressures were varied from the control, at approximately 160 mm Hg, to successively lower or higher pressures and returned to the control following each determination at the experimental pressure. Each point represents the data after the flow had stabilized at the new pressure.

as the perfusion pressure was varied from 40 to 100 mm Hg. These findings suggest that a vasodilator effect induced by the pump prevented the increase in vasomotor tone that occurs normally as perfusion pressure is increased from 35 to 85 mm Hg (76 and unpublished data). Autoregulation may be absent from kidney and skeletal muscle beds in the presence of strong extrinsic stimuli (69, 73, 111), and from intestine during the initial period of the perfusion (66).

AUTOREGULATION IN DIFFERENT VASCULAR BEDS. Autoregulation in brain has been both denied (22, 95) and supported (8, 26, 39, 71, 76). Autoregulation has been observed in the kidney by many investigators (58, 59, 65, 72, 97, 99, 105, 110, 116). Failure to note autoregulation when the kidney(s) is perfused via the aorta could be due to failure to ligate the two lumbar arteries that arise from the aorta between the right and left renal artery origins (58).

Fairly potent autoregulation was observed in skeletal muscle (27–29, 46, 109) and modest autoregulation in the intestine (66, 68, 101, 102) and in the liver (36, 92); but significant autoregulation was not elicited in skin (Rapela and Green, unpublished data). It would be anticipated that myocardium would demonstrate prominent autoregulation; however, to date this has not been demonstrated with certainty (17, 21, 24, 43, 84, 85, 98).

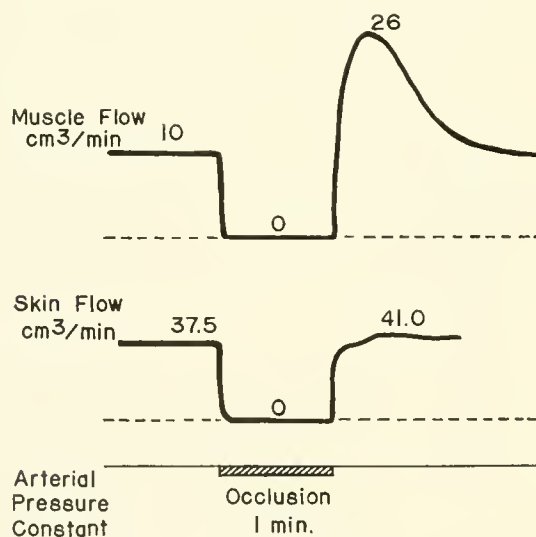


FIG. 11. Records of flow in a dog skeletal muscle vascular bed and in a cutaneous vascular bed (saphenous bed) before and following a 1-min period of occlusion of the arterial inflow. Arterial pressure upstream from the point of occlusion remained constant during these studies.

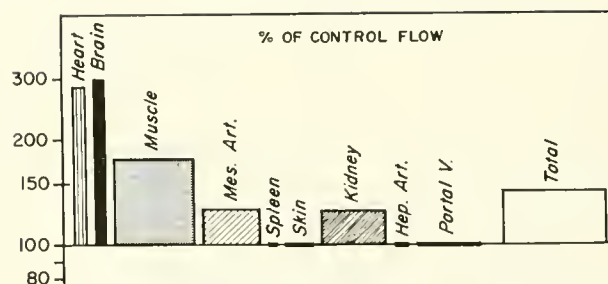


FIG. 12. Bar graphs of the magnitude of the reactive hyperemia computed from data such as that in fig. 11. The ordinate values are the maximum flow during the postocclusion period expressed as per cent of the control flow. The width of each bar represents approximately the proportion of the cardiac output which normally flows through the indicated vascular bed; total is the integrated effect for the body as a whole. [Reproduced from Green & Kepchar (45).]

REACTIVE HYPEREMIA. Occlusion of the arterial supply to a skeletal muscle bed for 30 sec to 1 min is followed, upon restoration of the original pressure, by a marked overshoot of flow (fig. 11, upper curve). This response has been thought to represent a local reaction of the arterial wall to changes in internal pressure (3). However, it is more likely that the overshoot represents a special manifestation of autoregulation. When muscle contracted during a period of occlusion the excess O_2 delivery during the period of reactive hyperemia underpaid the O_2 debt accumulated during the period of occlusion, if the muscle was at rest during the occlusion the reactive hyperemia overpaid the debt (9, 108).

Momentary overshoot of flow after a period of occlusion was noted on occasion in the dog's paw. However, comparison of weight changes (see below) with the integral of the flow during the period of overshoot suggested that the overshoot represented refilling of small vessels, which had emptied by elastic recoil into the vein during the period of arterial occlusion (114 and Rapela and Green, unpublished data).

Reactive hyperemia following temporary occlusion of the arterial supply is maximal in myocardium and brain (49, 84; and Rapela *et al.*, unpublished data), active in skeletal muscle, present in the mesenteric artery bed and in kidney, but is almost absent in spleen, skin (fig. 11, lower curve), hepatic artery, and portal vein vascular beds (45), as shown in figure 12.

MECHANISMS RESPONSIBLE FOR AUTOREGULATION. *Feed-back loop.* 1) General concept. The engineer's feedback loop provides a convenient way to visualize control mechanisms (fig. 13). The controlled variable is that

measurement which the controlling mechanism is attempting to keep constant (such as arterial pressure, or tissue O_2 tension). The level of the controlled variable may be disturbed by various loads, i.e., bleeding in the case of arterial pressure, or variations of tissue metabolism in the case of tissue O_2 tension. The detector senses continuously the magnitude of the variable and feeds the information to a summator or discriminator where it is compared with the desired value (set point) and modified by signals from other loops. The resulting signal is then fed to an effector which controls the activity of whatever process is necessary to maintain the controlled variable constant.

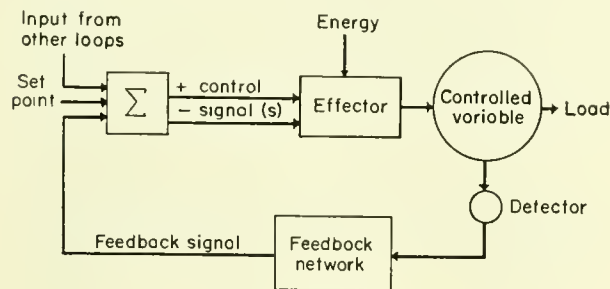


FIG. 13. Schematized diagram for a feedback loop (see text or discussion).

2) Present evidence suggests that, in skeletal muscle, a possible controlled variable in the feedback loop for autoregulation is the tissue oxygen tension (69). The detector is unknown; but the feedback loop may involve adenine formed from adenosine triphosphate (ATP) in the presence of insufficient oxygen. The summation point may be the receptor site on the arteriolar smooth muscle, and the effector may be the arteriole which controls the rate of blood flow by means of which the controlled variable is regulated (5).

3) There are other possible controlled variables in the feedback loop for autoregulation. The increased flow that occurs in skeletal muscle during and following a tetanic contraction may represent another manifestation of this pattern of autoregulation although axon reflexes in the sympathetic nerve supply have been postulated as playing a role (62). The vasodilation that occurs in skeletal muscle during activation of the patellar reflex is thought to be due to the same mechanism as that of the postcontraction hyperemia (107).

The controlled variable responsible for autoregulation (and reactive hyperemia) may vary with different vascular beds. Tissue oxygen tension appears to be the controlled variable in the myo-

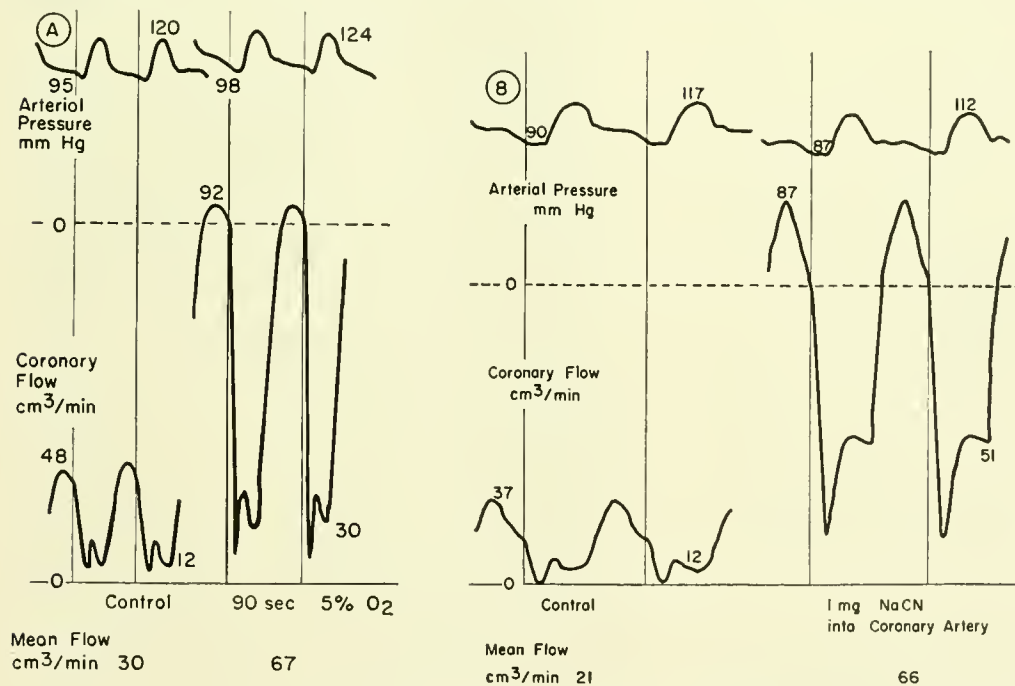


FIG. 14. Left anterior coronary artery inflows in the dog. A: in response to a 90-sec period of breathing 5% O_2 . B: effects of an intra-arterial injection of 1 mg of sodium cyanide. Note the calibration for flow is nonlinear (the deflection is approximately proportional to the square of the flow). [Modified after Green & Wegria (49).]

cardium and skeletal muscle, since reducing the oxygen content of the arterial blood produces a rather large increase in coronary (fig. 14A) and in skeletal muscle flow, whereas there is almost no change in flow in either bed when arterial blood CO_2 content is increased (12, 49). The fact that coronary flow is influenced more by coronary artery O_2 content than tension (51) is not incompatible with the concept that tissue O_2 tension is the controlled variable. The feedback loop in the heart must involve something other than O_2 tension, since intra-arterial injection of cyanide causes as great an increase of coronary flow as does hypoxia (fig. 14B) (49).

The increase in blood flow in the brain in response to decreased arterial blood oxygen content is relatively minor compared to that which follows an increase in CO_2 content (fig. 15) (44), suggesting that brain CO_2 tension may be the controlled variable for this tissue.

Elevation of arterial blood hydrogen ion concentration decreases resistance to flow through cutaneous (18, 25), renal (23), and skeletal muscle (18) vascular beds. Depression of the hydrogen ion concentration below normal is accompanied by increase of resistance to flow in skin (18, 25) and kidney (23); however, in skeletal muscle depressed hydrogen ion causes about the same degree of decrease of resistance to flow as

does an elevation of hydrogen ion concentration (18). Effects of hydrogen ion concentration on myocardial blood flow are reported to be the reverse of those in skin and kidney (38). These findings suggest that hydrogen ion might be one of the controlled variables in autoregulation.

Role of nervous system in autoregulation. Autoregulation is prominent in denervated vascular beds. High activity in the extrinsic nerves may even minimize or prevent manifestation of autoregulation; for instance, central reflex effects of hypoxia may overpower the local dilatory effect in the anesthetized dog's innervated skeletal muscle vascular bed (75) (see also p. 943). Autoregulation in kidney is not abolished by procaine anesthetization, adrenergic blocking agents, or gamma-aminobutyric acid (111), suggesting that the feedback loop contains no essential link that responds pharmacologically as does nervous tissue.

The behavior of cerebral blood flow in response to changes of perfusion pressure (see above) cannot be stated conclusively to represent strict autoregulation, since in these studies a reflex neural mechanism was not excluded. However, no influence of extrinsic autonomic constrictor nerves upon cerebral blood flow has been demonstrated conclusively (45), and therefore, it is unlikely that an autonomic reflex is involved in the cerebral studies.

Myogenic theory of autoregulation. Bayliss (3) proposed from studies of dog's hind legs and isolated arteries, that the arterial wall responds directly to a rise of intraluminal pressure by an increase in its state of contraction (or tone) sufficient to bring about a reduction in the lumen of the vessel (and presumably therefore, a decrease in the flow through the vessel). This concept received support from Johnson (66) who failed to find an appropriate correlation between change in the O_2 concentration of the venous blood draining an isolated segment of gut and the occurrence of a decreased resistance to flow as perfusion pressure was lowered. Since he found, also, no correlation with nerve activity, gut contraction, or presence of metabolites, Johnson concluded that the autoregulatory change of flow represented a myogenic response. Waugh & Shanks (111) observed that hypothermia (3–10 C), intrarenal infusion of chloral hydrate, or high concentrations of procaine abolished autoregulation but that anoxic perfusion did not depress the autoregulatory reaction; since nerve block also did not interfere (see above) they concluded that renal autoregulation is due to "myogenic vasomotion." Folkow (27) also postulated a myogenic

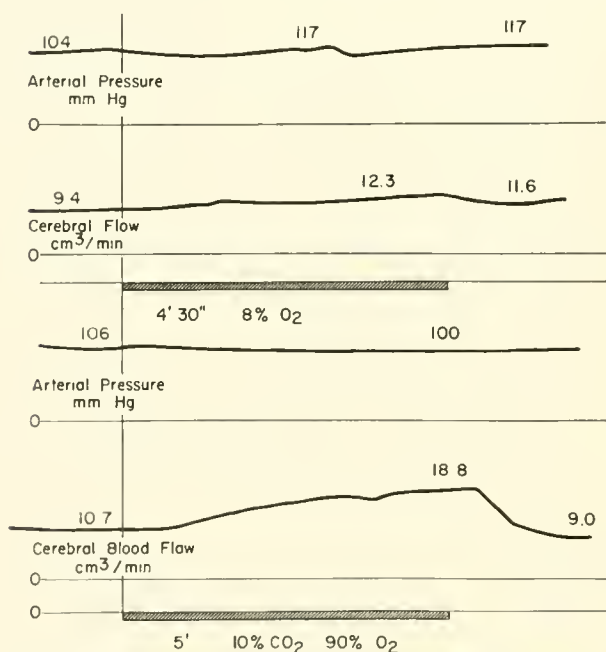


FIG. 15. Records of cerebral venous outflow and systemic arterial pressure during a 4.5-min period of breathing 8% O_2 (upper pair of curves) and in response to a 5-min period of breathing 10% CO_2 in 90% O_2 (lower pair of curves) in the dog. Brain was perfused directly from the aorta.

basis for autoregulation in skeletal muscle since it was not abolished by breathing oxygen at either high or low partial pressure. It should be noted that the above conclusions regarding the myogenic theory are based solely on negative evidence. It seems quite unlikely to us that a vascular wall could respond appropriately to changes of intraluminal pressure per se.

Physical factors related to autoregulation. Renal blood flow at a given level of arterial pressure was the same whether the perfusion pressure was steady or pulsatile. Autoregulatory changes in resistance were observed with both types of perfusion (93).

A rise in renal interstitial and intrarenal venous pressure was found to parallel an elevation of arterial pressure over the "autoregulatory range." This finding is proposed as the explanation for the autoregulatory rise in renal vascular resistance that accompanies an elevation of renal arterial pressure (65, 96). On the other hand, two other groups of investigators (81, 111) could not account for the observed autoregulation in their dogs' kidneys on the basis of such changes in intrarenal tissue or venous pressures.

An increase in postglomerular viscosity which parallels glomerular filtration rate (116) has been proposed to explain the "autoregulatory" increase in renal vascular resistance that accompanies a rise of arterial perfusion pressure above 80 mm Hg. However, Selkurt *et al.* (100) found that arterial perfusion pressure could be varied between 100 and 160 mm Hg without significant change in blood flow (para-minohippurate clearance), glomerular filtration rate (creatinine clearance), or filtration fraction. In their experiment, therefore, the postglomerular viscosity remained unchanged, and the autoregulatory variation in renal vascular resistance must have occurred solely in the preglomerular vessels. An increase in effective viscosity of the blood flowing in the cortical layers due to plasma skimming in the intralobular arteries (cell separation theory) has been proposed by Pappenheimer & Kinter (72, 87) to explain renal autoregulation. However, Waugh & Shanks (111) were able to demonstrate autoregulation in the kidney using a cell-free perfusate, so long as the fluid contained plasma. Evidently simple physical phenomena will not serve to explain renal autoregulation.

Enlargement of collateral communications following occlusion of the cognate arterial supply as a manifestation of autoregulation. It is well known that, following occlusion of an artery, collateral communications between the cognate bed and collateral arteries enlarge rapidly

until within a few hours to weeks they can supply almost a normal rate of flow to the cognate bed. Such enlarged channels are demonstrated beautifully during arteriography. The dilation of the communicating channels may be considered a special case of autoregulation, although almost nothing is known regarding its mechanism of action. It does not appear to be brought about by any special change in arterial pressure proximal to the occlusion. The enlargement of the communicating channels is more likely related to an increased rate of flow or enhanced pressure drop through the communicating channels (60).

Summary of present status of feedback control of autoregulation. Though the mechanism of the autoregulation of blood flow has not been established as yet, the following trends may be stated. *a)* Most likely there is more than a single factor involved and the predominant one may vary in different organs. In the kidney, for example, maintenance of a constant glomerular filtration rate may be more significant than satisfaction of the metabolic requirements of the organ; consequently the sensing mechanism to regulate blood flow should be related directly or indirectly to glomerular filtration. The juxtaglomerular apparatus may serve this function (97, 111). In organs such as a skeletal muscle and the heart, metabolism fluctuates rapidly; in these a mechanism must be available to allow adaptation of flow to the varying metabolic demands. Such mechanism should be capable of sustaining the metabolic activity in the face of fluctuations in arterial pressure. In either case the sensing mechanism may detect the adequacy of supply (i.e., tissue O_2 tension) or the adequacy of removal of metabolic products (i.e., tissue CO_2 tension). It appears probable that the former is sensed in heart and muscle and the latter in the brain. *b)* Autoregulation may be absent in vascular beds such as the paw or skin which have very low metabolic requirements. *c)* Whatever the mechanism of autoregulation, at times it appears to be dependent on the presence of certain "normal factors" in plasma required for maintenance of "normal vascular tone," and at other times to be masked by certain "abnormal factors" which may induce either "abnormally high" or "abnormally low vascular tone."

INTERPRETATION OF CHANGE OF VASOMOTOR TONE INDUCED BY CONSTRICTOR AND DILATOR AGENTS IN VASCULAR BEDS WHICH DEMONSTRATE AUTOREGULATION. *In artificially perfused beds.* When studying responses to vasoconstrictor and vasodilator stimulation in a vascular bed which demonstrates autoregulation it may

be advantageous to use a constant-flow technique. This is particularly the case if the autoregulation is operating to maintain flow in proportion to metabolic need. Under these circumstances the change in arteriovenous difference of pressure probably will reflect the action of the infused agent with a minimum of complication. On the other hand, if constant pressure perfusion is used the autoregulatory mechanism may mask the effect of the vasoactive agent by providing a counterdilation or constriction in an attempt to maintain flow constant (see p. 940).

Interpretation of change of vasomotor tone in autoperfused vascular beds. Intravenous infusion of a constrictor agent which raises systemic arterial pressure may fail to alter blood flow in a vascular bed showing autoregulation. This lack of response may be interpreted incorrectly as indicating that the agent has exerted a vasoconstrictor effect. Such misinterpretation has been made in the case of the cerebral vascular bed. In such instances the vasoactive agent should be injected directly into the arterial supply to the vascular bed. If there should be no response to the intra-arterial injection then the lack of response during the rise of systemic arterial pressure with intravenous injection of the agent would be due to local autoregulation. In this case the vascular bed would be attempting to maintain flow constant despite the rise of arterial pressure (90b).

Chemical Effects on Resistance Vessels

Hypertonic solutions (above 5% NaCl) decrease the resistance to flow in systemic vascular beds (56)

by an unknown mechanism, but increase that in the lung. The latter seems to be due to intravascular red cell agglutination (91).

Potassium and magnesium ions cause active limb arteriolar dilation, calcium induces constriction (54) while sodium has little effect (86). Acetate, among the anions, produces arteriolar dilation (82).

Extrinsic Control of Resistance Vessels

EFFECTS OF VASOACTIVE AGENTS ON TOTAL RESISTANCE IN A VASCULAR BED. Extrinsic control of resistance vessels, i.e., of the peripheral resistance in the various vascular beds is illustrated most typically by the responses in a skeletal muscle vascular bed, since reactions, characteristic of all beds, are present in this bed. In a skeletal muscle bed, intra-arterial injections of epinephrine and of levarterenol cause a marked decrease in flow followed, often, by a secondary rise above control level (fig. 16). Such response occurs characteristically after all injections of levarterenol and after injections of 1 μ g or more of epinephrine. Smaller amounts of epinephrine often induce either no response or an increase in flow indicative of vasodilation. Lumbar sympathetic chain stimulation usually decreases flow (fig. 16), although occasionally an initial increase followed by decrease or solely an increase in flow occurs (30, 45, 117).

After induction of adrenergic blockade (fig. 16), levarterenol may have no effect or may cause a slight increase in flow while both epinephrine and lumbar sympathetic chain stimulation increase flow. Atropine injected intra-arterially abolishes the increase in flow

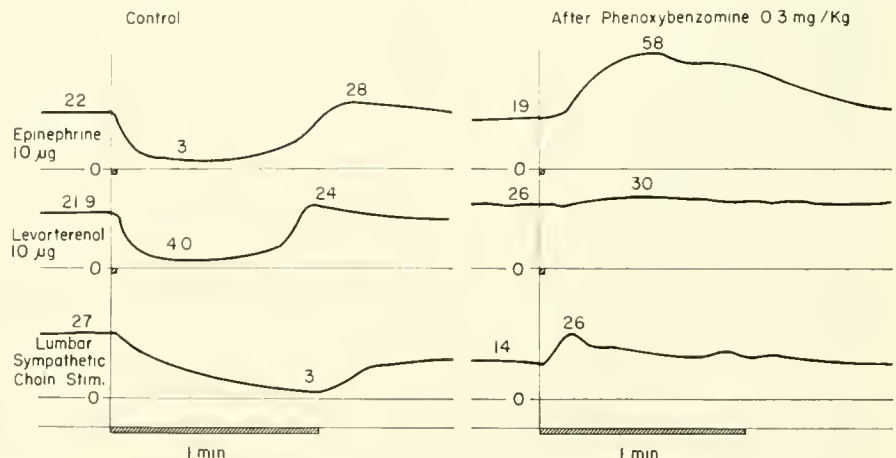


FIG. 16. Curves of arterial inflow in a skeletal muscle vascular bed in the dog in response to intra-arterial injections of 10 μ g of epinephrine, 10 μ g of levarterenol (norepinephrine), and a 1-min period of stimulation of the lumbar sympathetic chain, during a control period (left half) and after an intra-arterial injection of 0.3 mg/kg of phenoxybenzamine (right half). Flow measured in ml/min; arterial pressure remained constant through the study. [Modified after Youmans *et al.* (117).]

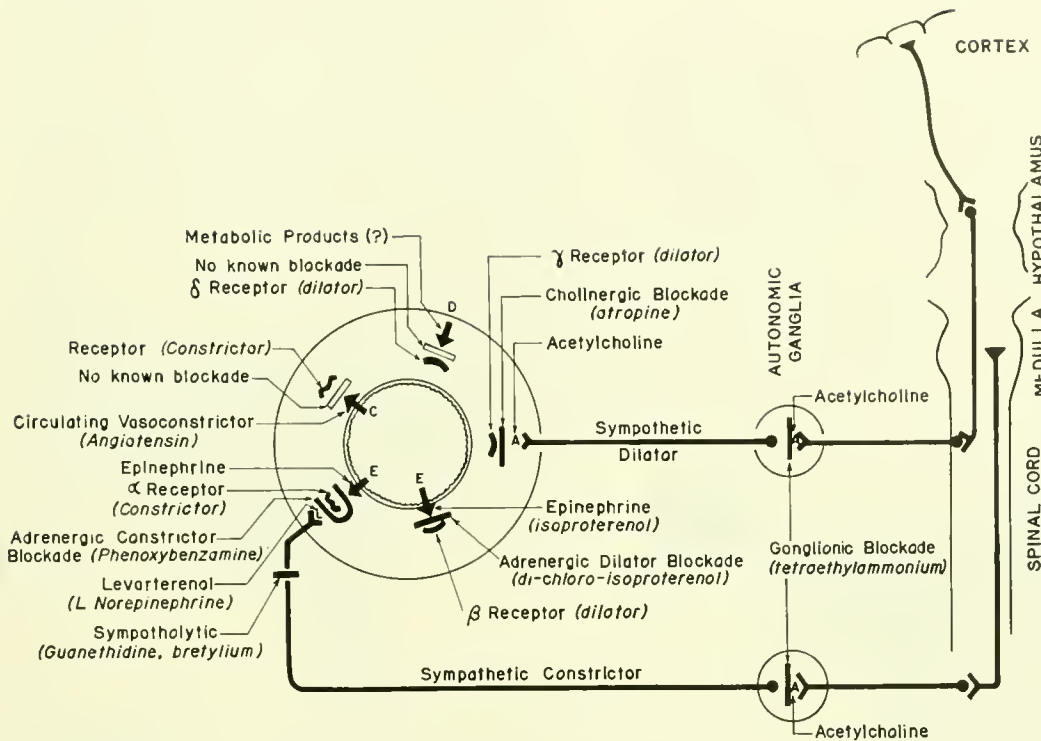


FIG. 17. Diagram of hypothetical receptor sites on arterioles in skeletal muscle. (See text for discussion.) [Modified from Green & Kepchar (45).]

induced by lumbar sympathetic chain stimulation, but has essentially no effect upon the dilator response to epinephrine (45, 90a, 117).

On the basis of detailed studies similar to the above, Ahlquist (1) proposed that two adrenergic receptors are present in blood vessels controlling the resistance to flow in vascular beds (fig. 17). The first of these has a constrictor (excitatory) action on vascular smooth muscle; but because it has an inhibitory action elsewhere (notably in the gut) it was not referred to as an excitatory receptor but, noncommittally, as the alpha receptor. It is blocked by phenoxybenzamine and similar adrenergic blocking agents. The second type of receptor causes relaxation of vascular smooth muscle but because it has an excitatory effect on the heart it was denoted as the beta receptor. It is blocked by dichloroisoproterenol. The alpha receptor is most sensitive to epinephrine, and least sensitive to isoproterenol, whereas the beta receptor is most sensitive to isoproterenol and least sensitive to arterenol.

We would prefer to limit the term alpha receptor to those receptors which are located on blood vessels. As such the alpha receptor would always be constrictor and innervated by sympathetic nerve fibers. We

would prefer also to limit the beta receptor to vascular sites. As such it would always be inhibitory (vasodilator) and to the best of our knowledge never innervated.

In addition to these two adrenergic receptors of Ahlquist, other vascular receptors have been proposed (45). A third group, the gamma dilator receptors, are excited by acetylcholine and by stimulation of sympathetic dilator fibers and blocked by cholinergic blocking agents such as atropine (45). A fourth possible group, the delta dilator receptors, may be excited by metabolic products or low tissue O_2 tension; they are probably the receptors which participate in autoregulation and reactive hyperemia. At present no agents are known which block the delta receptors. Several more receptors are probably present; those receptors, which respond to constrictor agents such as angiotensin, vasopressin, and similar polypeptides, are grouped together under the term "epsilon constrictor receptors"; no agents are known which can block these receptors.

The potency of various agents in inducing constriction or dilation varies from one vascular bed to another. Cerebral and cardiac vascular beds show essentially no constrictor response to adrenergic

agents, whereas all other beds show a significant response (fig. 18). Secondary dilation and the dilation following adrenergic blockade which occur with epinephrine are due probably to excitation of beta receptors; this effect is of significant magnitude in skeletal muscle bed and of lesser magnitude in cardiac, mesenteric arterial, and splenic vascular beds (fig. 19).

Sympathetic constrictor fibers exert maximal effects in kidney, skin, and mesenteric beds. Significant constriction is noted in muscle, spleen, and hepatic

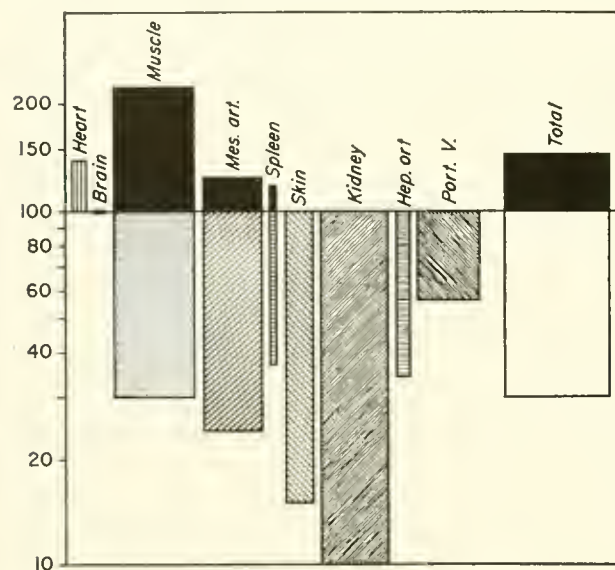


FIG. 18. Bar graph of responses in various vascular beds to an intra-arterial injection of 1–10 μ g of epinephrine. Light-colored bars—initial responses; dark-colored bars—secondary (dilator) responses. See legend to fig. 12 for additional information. [Reproduced from (45).]

arterial and portal venous beds; but no significant reduction of flow occurs in cerebral or cardiac beds (fig. 20).

In the dog, unequivocal cholinergic dilator responses in response to sympathetic nerve stimulation are seen only in skeletal muscle (fig. 20) (45). However, Beck & Brody (4) believe that another active dilator pathway can be demonstrated in the dog's hind quarters perfused at a constant rate of flow. Dilation, primarily induced by this pathway, is most readily obtained by release of tracheal occlusion and is not blocked readily by atropine. It is claimed that in man there is a cutaneous vasodilator innervation (61, 94). It is claimed also that when sweat fibers are activated there is a release of bradykinin which causes secondary dilation in blood vessels adjacent to the sweat glands (34). However, Senay *et al.* (103) often found marked dissociation between sweating and vasodilation in the forearm.

SEGMENTAL RESISTANCES IN VASCULAR BEDS

Methods

The behavior of the small vessels, i.e., the arterioles and venules, may be inferred from comparison of the pressures recorded from fine catheters fed distally into small arteries and veins via the large vessels, with the lateral pressures recorded from the larger vessels (53, 57). Additional information is yielded when flows are measured simultaneously (14, 15). Micro-puncture studies have been used to obtain the pressures in the portal venous tree, portal venules, and central veins of the liver (83).

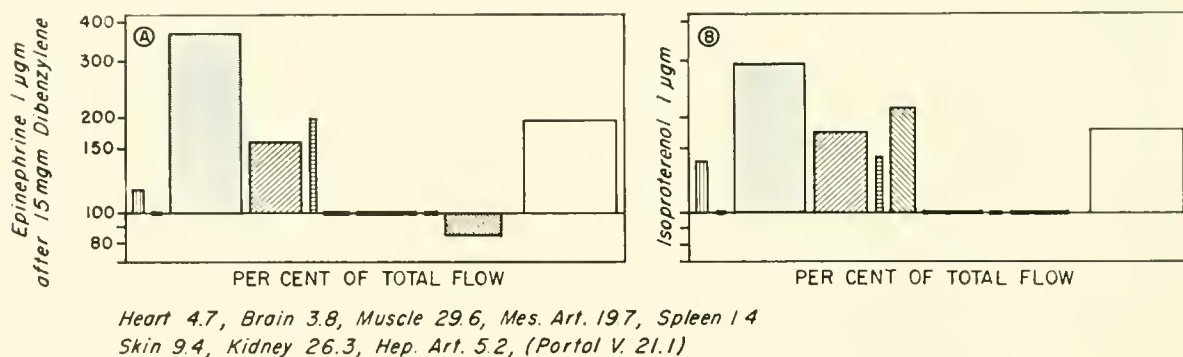


FIG. 19. Bar graphs of responses to intra-arterial injections of isoproterenol (B) compared with those to epinephrine during adrenergic blockade with phenoxybenzamine (Dibenzylene) (A). The ordinate values are the maximum flows in response to the agent, expressed as per cent of the control flow. The last bar (unshaded) represents the computed integrated effect on the total body flow (cardiac output). The sequence of the bars appears in the figure; the figures on the abscissa represent the per cent of cardiac output which flowed through the bed in the control period. See legend to fig. 12 for further explanation. [Reproduced from (45).]

Effects of Changes of Perfusion Pressure and of Venous Pressure on Large Artery and Vein, and Distal Small Vessel Pressures

In general, when perfusion pressure is varied while other factors remain constant, pressure in the small vessels parallels that in the large vessels (fig. 21).

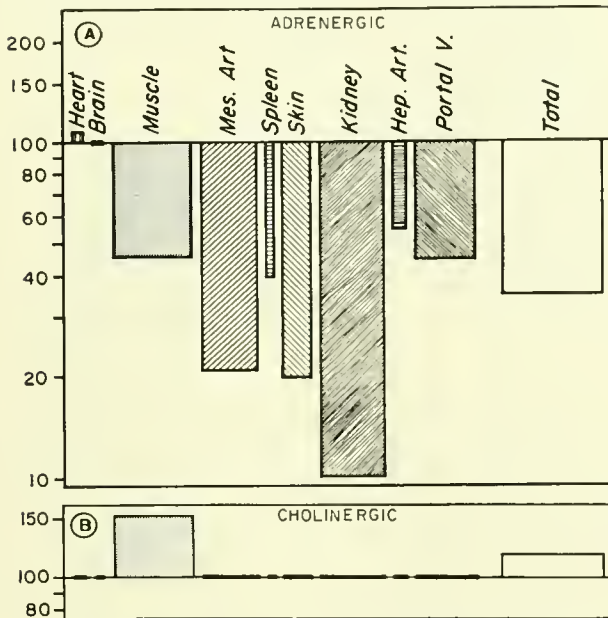


FIG. 20. Bar graph of responses to stimulation of sympathetic constrictor nerve supply (A) and of sympathetic dilator nerves (B). The ordinate values give the flow at the moment of maximal response to the stimulation, expressed as per cent of the control flow. See legend to figs. 12 and 19 for further explanation. [Reproduced from (45).]

Elevation of an intestinal large vein outflow pressure leads to a progressive increase in the venous volume (yielding a measurable venous compliance), to a decrease in the venous resistance, to a progressive elevation of capillary pressure, and to a slower change in gut volume due to capillary filtration (67).

Effects of Extrinsic Agents on Segmental Resistance

Decrease in CO_2 tension and hydrogen ion concentration, produced by hyperventilation, induced dilation of the arteries with concomitant constriction of small vessels in intact forelegs. Opposite changes in both vessel segments were induced by increased CO_2 tension and hydrogen ion concentration. Serotonin decreased small artery pressure markedly associated with an increase in small vein pressure and no change in large artery and vein pressure or total resistance [Haddy (52)]. These findings suggest that serotonin exerts its effects predominantly on vessels larger than the arterioles and venules.

Intra-arterial infusion of epinephrine into the dog's paw caused the large artery to small vein pressure difference to increase as flow decreased (fig. 21C). Simultaneously, the small vein to large vein pressure difference decreased with flow in about the same degree as that which had been noted during control studies in which perfusion pressure had been lowered progressively (fig. 21A). Subsequently, large artery to small vein pressure difference decreased, and flow rose, but small vein to large vein pressure differ-

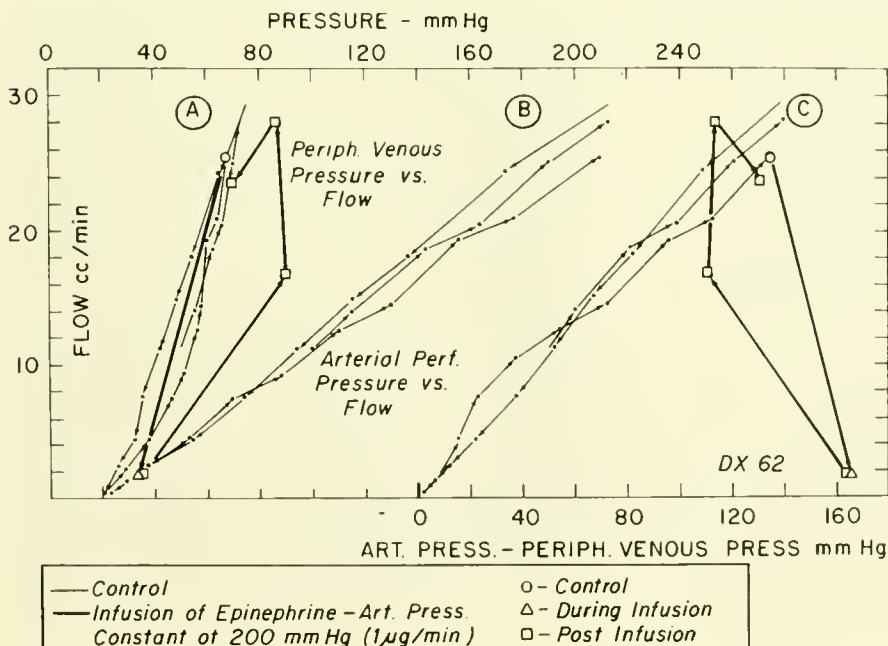
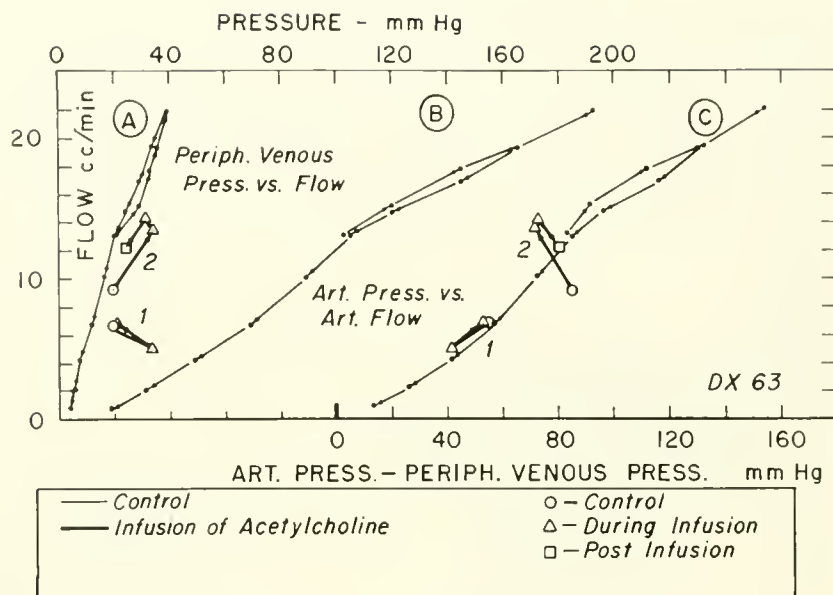


FIG. 21. Plots of relationship of blood flow in the dog's paw to pressure. A—flow vs. the difference between distal small vein and large vein pressure; B—flow vs. the large artery to large vein pressure difference; C—flow vs. large artery to distal small vein pressure. Heavy lines—successive responses to an intra-arterial infusion of 1 µg/min of epinephrine while the perfusion pressure was held constant at 200 mm Hg. Abscissal values for C = abscissal values for B minus abscissal values for A. Distal small vein pressures were recorded from an 0.5-mm polyethylene catheter inserted into a superficial vein and passed as far distally as it would go.

FIG. 22. Plots similar to those in fig. 21 showing the responses to an intra-arterial infusion of acetylcholine at the rate of 25 $\mu\text{g}/\text{min}$, 1; and to an intra-arterial infusion of acetylcholine at the rate of 100 $\mu\text{g}/\text{min}$, 2. Arterial pressure was held constant at 75 mm Hg for 1, at 105 mm Hg for 2.



ence increased. These findings suggest a dual effect of epinephrine, i.e., an initial small artery or arteriolar constriction, or both, and a subsequent small to intermediate vein constriction as the arterioles dilate [(55) and Rapela and Green, unpublished data]. Similar changes were recorded in dog's leg during sympathetic stimulation (13).

Acetylcholine, infused into a dog's paw, caused effects opposite from those of epinephrine. Small doses had no effect on the arterioles (fig. 22C, 1) but increased the small vein resistance (fig. 22A, 1); larger doses decreased the arteriolar resistance (fig. 22C, 2), but only slightly increased small vein resistance (fig. 22A, 2) [(52) and Rapela and Green, unpublished data].

Intermediate artery and vein behavior has been studied by inserting fine (0.5 mm) catheters centrally into a small artery and a small vein at the dog's ankle and recording the pressures during a control state and during strong stimulation of the peripheral homolateral lumbar sympathetic chain (15, 70). During stimulation pressure in the small artery fell dramatically while that in the small vein rose. These findings suggest a marked increase in the resistances to flow in the artery and vein between the points of cannulation and the more proximal points of pressure measurement in the larger arteries and veins. The stimulations were repeated as the catheters were fed into the artery or vein toward the knee (15). In the control state the arterial pressure was the same at all levels of the catheter tip but, during sympathetic

stimulation, a marked drop in pressure was noted in the artery at all points distal to 15 cm proximal to the ankle. These findings indicate that strong vasoconstriction occurred in the arterial tree midway between knee and ankle sufficient to stop flow and pulsations. Similar closures were recorded in the veins midway between knee and ankle. The morphological background for this was described by Shadle *et al.* (104); they noted that the dorsal foot veins were thick walled and difficult to distinguish from small arteries while veins from thigh muscles were thin walled.

In a subsequent paper, Davis & Hamilton (16) studied the responses further by a "cross-perfusion" method which allowed the blood to flow out of the proximal cut end of a small artery of the foot through a flowmeter and into the distal cut end of the corresponding artery of the opposite foot. Similar cross perfusion was arranged in the veins. Thus stimulation of the sympathetics on one side could affect flow only by causing constriction of the intermediate size vessels proximal to the ankle, whereas, stimulation of the sympathetic fibers on the opposite side of the body could affect flow only by causing constriction of small distal arteries, arterioles, venules, and small distal veins. They found that sciatic nerve stimulation produced intense constriction in both proximal intermediate and distal small arteries and veins which, in either case, was sufficient to stop flow. Lumbar sympathetic stimulation produced similar effects but they were slightly less intense in the paw than with

sciatic nerve stimulation. Incidentally, they noted that retrograde flow could be induced in the distal small vessels from vein to artery when these were not being stimulated, and the arterial pressure was low.

It should be noted that Davis and Hamilton speak of recording "small vessel" pressures, but it is our interpretation that the data indicate the role of intermediate vessels as well as arterioles and venules. It remains to be demonstrated whether the above observations represent a response that might occur under reasonable degrees of physiologic stress or a change that would occur only under unusual conditions such as intense electrical stimulation of the sympathetic chain. Effects such as these were significantly less marked in the intermediate vessels supplying the rabbit ear during stimulation of the third cervical nerve or the ipsilateral cervical sympathetic trunk (14).

BLOOD VOLUME IN VASCULAR BEDS (VASCULAR CAPACITY)

Methods

The volume of the various components of the vascular bed has been studied by injection techniques (77). The volume in a given vascular bed can be computed also by ligating abruptly the artery and vein, washing out the contained blood, measuring the hemoglobin content of the washout and comparing this with the hemoglobin content of the blood perfusing the bed.

Estimates of vascular capacity in an intact bed can be made by intra-arterial injection of an indicator with determination of the time course of the indicator concentration in the venous effluent (42). A typical record (fig. 23) shows an abrupt rise in the indicator concentration, beginning about 5 sec after the injection; the concentration reaches a peak in 10 sec and then returns to control level at approximately 90 sec. The rate of flow can be computed by dividing the milligram of indicator injected by the area under the indicator concentration curve, expressed in $\text{mg} \cdot \text{sec}/\text{ml}$ (fig. 23, *C* and *D*).

Curves *A* and *B* in figure 23 show the integration of the indicator concentration curve. By integrating the area above and to the left of the upper curve and dividing this area by the height of the curve, the mean transit time of the indicator through the vascular bed can be obtained. Multiplication of the mean transit time by the rate of flow gives the volume in the vascular bed. In this experiment on the paw, flow was 26.5 ml per min (0.44 ml sec), mean transit time 21.2 sec, and vascular volume 9.35 ml. Comparison of the flow measured with the indicator concentration curve with that measured simultaneously with the electromagnetic flowmeter shows the former to average 103 per cent (SD 4.6) of the latter. Correlation of the last determination of vascular volume with the vascular volume determined by the hemoglobin washout method shows that the former averaged 94 per cent (SD 38.5) of the latter (48).

Effects of Various Factors on Vascular Volume

In a set of experiments on the dog's paw, changes in perfusion pressure produced approximately proportional changes in flow (fig. 24), whereas mean transit time varied inversely. As a consequence neither vascular volume nor conductance ($1/\text{resistance}$) was altered to any significant extent. Acetylcholine,

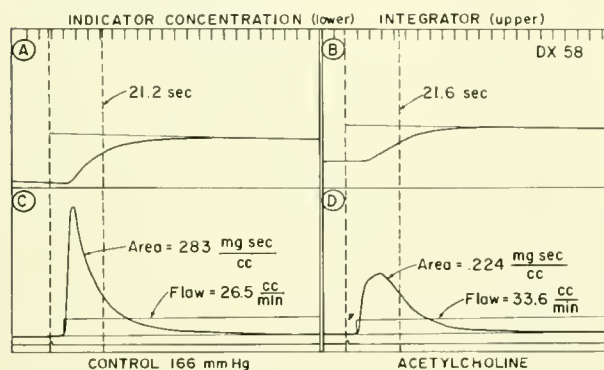


FIG. 23. Records obtained from the dog's paw showing the time course of the concentration of an indicator (indocyanine green) recorded in the venous outflow following an intra-arterial injection of the indicator. *C*, *A*: curve recorded from the output of an integrator whose input was the output from the indicator concentration recorder. Time lines at the top—5 sec. *B* and *D*: similar records obtained during an intra-arterial infusion of acetylcholine, which were recorded after a stable rate of flow had been attained. Perfusion pressure 116 mm Hg for all four curves. In each case, 0.125 mg of indicator was injected as a square-wave pulse during a 1-sec period. The upper asymptote was drawn parallel to "integrator base line." The slight inclination of the latter was due to a failure to balance the integrator to the densitometer output when control blood was flowing through the cuvette. A 2- to 3-sec delay is noted between the beginning movement of the densitometer and the beginning movement of the integrator pens. This is due in part to the lag of the recorder and possibly to slight delay in the integrator. It is corrected in the calculations since the true mean transit time is obtained by subtracting the delay time from the apparent mean transit time. The delay time is obtained by making a second injection at the sampling site in the venous outflow.

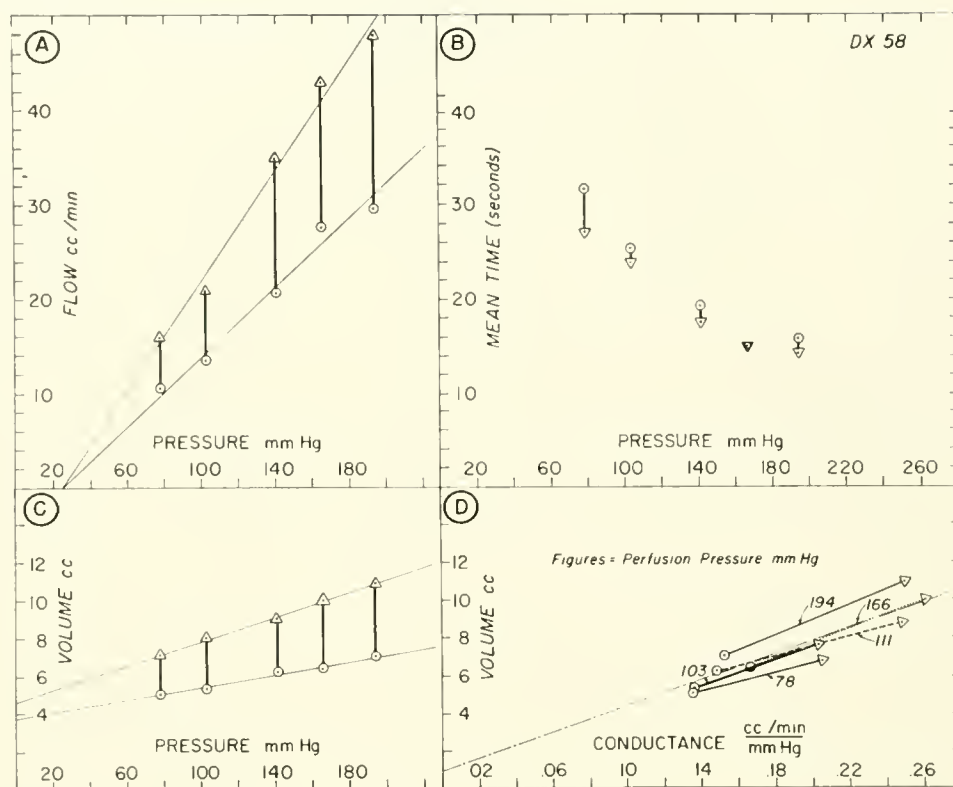


FIG. 24. Effects of perfusion pressure per se (circles) and of an infusion of acetylcholine at each level of perfusion pressure (triangles) on flow, mean transit time, volume, and conductance in the dog's paw. Same experiment as that in fig. 23. *A*: plot of perfusion pressure (arteriovenous difference of pressure) vs. flow. [In a larger series of experiments the pressure-flow relationship in the vascular bed of the paw was best represented by a curve with convexity towards the pressure axis, when plotted in linear coordinates, similar to that observed in the skin (fig. 3)]. *B*: plot of perfusion pressure vs. mean transit time. *C*: plot of perfusion pressure vs. vascular volume (computed from product of flow \times mean transit time). *D*: plot of conductance vs. vascular volume. Figures in *D* represent the perfusion pressures used for each pair of determinations.

infused intra-arterially in this experiment had similar effects at all levels of perfusion pressure. This agent increased flow and, thereby, lowered the amplitude of the indicator concentration curve (fig. 23). However, mean transit time did not change appreciably and therefore vascular volume and conductance were both increased, the latter proportionately more than the former (fig. 24). The straight-line relationship between flow and pressure may indicate a considerable though not maximal dilation of the arterioles (p. 937).

When using indicators it is necessary that a stable state exist since, if the volume is changing during the determination, a false reading will be obtained. When this occurs, the flow computed by the indicator method may differ significantly from that recorded simultaneously by a flowmeter.

ESTIMATION OF CHANGE OF VASCULAR VOLUME DUE TO EXTRINSIC INFLUENCES

Changes in vascular volume in an organ may be measured by recording continuously the organ's weight or its volume with a plethysmograph. These methods give the relative change of vascular volume but not the actual volume of blood in the bed at any moment. Changes in vascular volume measured by these methods may be used to confirm changes in volume obtained with the indicator method. Comparison of change of vascular volume with simultaneously recorded blood flow gives an indication of the interplay of resistance and capacitance vessels (31, 80).

Different vascular beds vary significantly in their response to factors causing a change of vascular

volume. In response to intra-arterial epinephrine the vascular volume in the dog's paw tends to decrease as the resistance to flow increases, i.e., as flow decreases.

During constant-flow perfusion of the isolated dog's hind quarters intra-arterial perfusion of levarterenol caused *a*) a marked rise in the perfusion artery pressure (increased resistance to inflow through the arterioles); *b*) a decreased venous outflow; and *c*) a rise in limb weight (due to distention of the arteries proximal to the site of constriction). When the rising arterial pressure overcame the arteriolar resistance outflow increased above inflow and limb weight fell despite persistence of the elevated arterial pressure. The authors concluded that the latter effect was due to translocation of blood by constriction of the veins. Because of the small changes of T-1824 and P³² tag concentrations, they concluded also that only a very small percentage of the leg weight change was due to transcapillary movement of either plasma or interstitial water (104).

Reductions in flow and volume were noted in cat's hind legs in response to levarterenol; this finding was interpreted as being due to constriction of both the "resistance" and the "capacitance section" of the vascular bed (31, 80). In this preparation intra-arterial epinephrine caused an initial increase in outflow simultaneously with a decrease in volume, whereas isoproterenol and acetylcholine increased both flow and volume. Since levarterenol seemed to be more potent than angiotensin in reducing the volume of blood contained in the capacitance section of the hind leg (muscle and skin) of cats, Folkow *et al.* (33) claimed that a greater constrictor effect on

the capacitance vessel (larger veins) is exerted by levarterenol than by angiotensin. As we visualize it, the data should be interpreted oppositely, i.e., that angiotensin has a more potent effect than does levarterenol on the postcapillary, or a less potent effect on the precapillary vessels (see below).

The vascular volume of the spleen decreased more rapidly and abruptly than the inflow in response to intra-arterial epinephrine, levarterenol, or sympathetic nerve stimulation. After a period of time the inflow began to increase rapidly exceeding outflow and resulting in a progressive augmentation of spleen weight (47) (fig. 25).

The usual accompaniment of an increase in vascular resistance of an organ is a decrease in its volume as measured plethysmographically or by weight changes. This change is the result of a diminution of the volume of the resistance vessels (arteriolar constriction) and perhaps more importantly the lessening of the distention of the postarteriolar vessels and even the closure of some of the capillaries and venules (fig. 26). Only rarely is an increase in resistance accompanied by an increase in organ volume. When this occurs, it is due probably to a preponderance in the resistance increase of postcapillary or even venular vessels over that occurring in the precapillary vessels, thus causing an increase in upstream (capillary) pressure which may lead to an augmentation of organ volume by distending the capillaries (fig. 26) and by increasing the filtration of fluid into extravascular spaces. The kidney is the only organ in which a well-documented increase in volume accompanies an increase in resistance. That this is due in part to an increase in

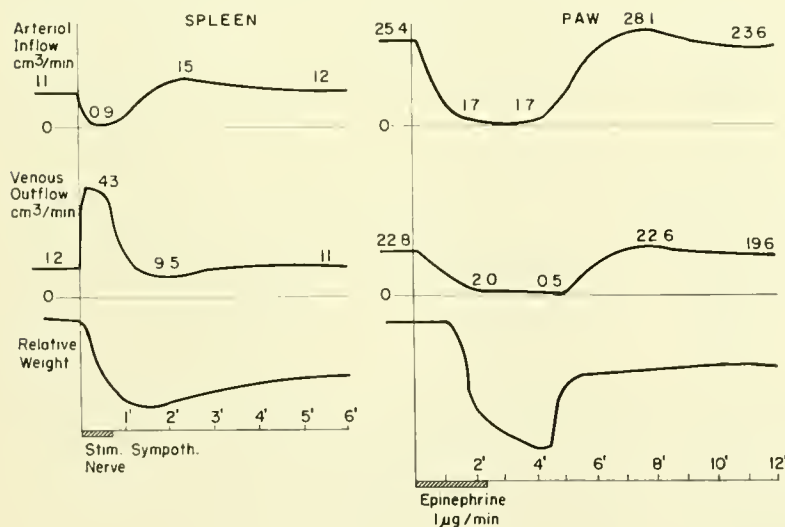


FIG. 25. Records of arterial inflow, venous outflow, and relative weight changes of the dog's spleen in response to stimulation of sympathetic nerve supply and of the dog's paw in response to slow intra-arterial infusion of 1 μ g/min of epinephrine. [Modified after Green *et al.* (47).]

intravascular volume rather than an increase in extravascular volume (106) has been shown by Mehrizi and Hamilton (79) using calculations from mean transit time. It has been attributed classically to constriction of efferent glomerular arterioles and a passive distention of upstream vessels.

In short, changes in vascular volume as a result of increased resistance to flow can be attributed to any combination of three causes, all operating at the same time: 1) decreased volume of constricting vessels, 2) decreased distention of downstream vessels, and 3) increased distention of vessels upstream to the site of preponderant increase in resistance. The net change in vascular volume will, then, depend on the location

of the resistance increase in the morphological pattern of the vascular network. A lessening of resistance in any part of the network will presumably induce opposite changes in vascular volume. These structures are affected differentially by various vasoactive agents. Data are insufficient at present to draw significant generalizations regarding the various vascular beds.

PULSATILE CHANGES IN VASCULAR VOLUME

Pulsatile flow through a dog's ulnar artery was measured with a square wave electromagnetic flowmeter together with pressure recorded in a small branch just proximal to the flowmeter and with paw volume pulse recorded plethysmographically (fig. 27). The flow record showed a dicrotic notch but never fell to or below zero during diastole. A volume pulse calculated by integrating the flow pulse and subtracting an assumed constant venous output was essentially similar (fig. 27). Both showed two humps of approximately similar magnitude.

In man, the normal digital volume pulse rises relatively more rapidly than that of the dog's paw, has a sharp peak at the end of the first quarter of the pulse interval, and a slight notch about halfway down the descending limb (fig. 28). If the supplying artery is occluded but adequate collateral circulation is available, the digital pulse shows a peak which is rounded and delayed, and the notch on the descending limb is absent. In the presence of vasospastic disease, the peak may be delayed slightly, the notch raised or may occur sooner on the descending limb, and the area of pulse per unit amplitude increased in comparison with the normal. With elevation of venous pressure or interference with venous outflow, the peak of the pulse is sharper than normal and a second hump

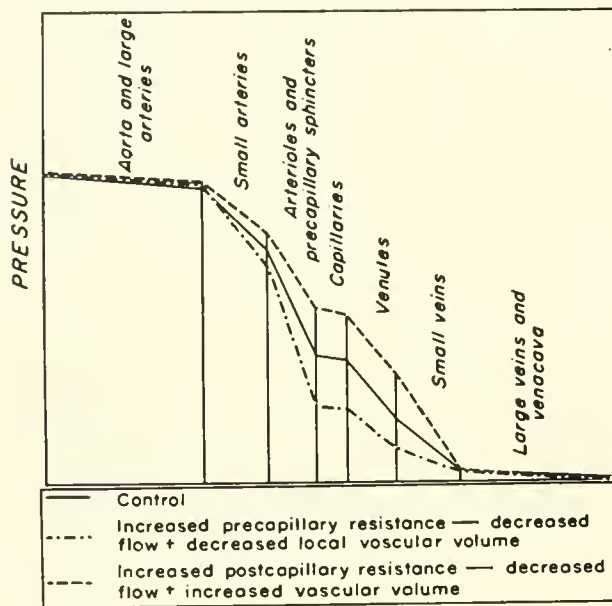


FIG. 26. Hypothetical plots of the pressure drops in various portions of the terminal vascular bed during a control state, solid line; during a state of increased precapillary resistance, dash-dot line; and increased postcapillary resistance, dashed line.

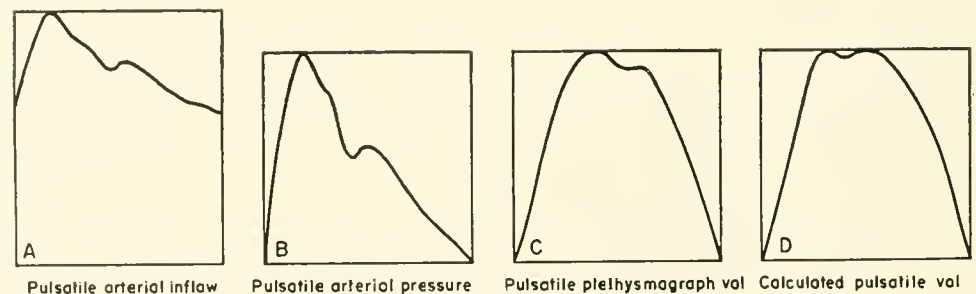


FIG. 27. Records of A—pulsatile arterial inflow; B—pulsatile arterial pressure; and C—pulsatile plethysmographic volume, in the dog's paw. Arterial inflow recorded with an electromagnetic meter on the ulnar artery. D—pulsatile volume calculated from the pulsatile arterial inflow, assuming a constant venous outflow.

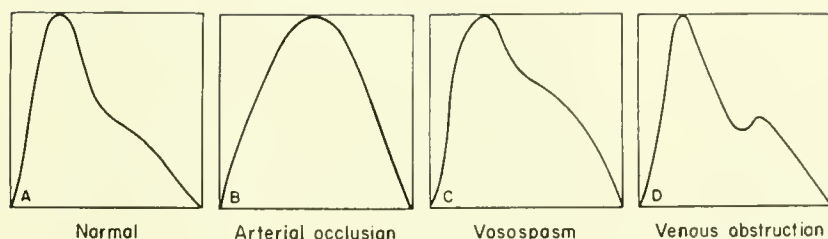


FIG. 28. Averaged plethysmographic pulses from the digits of patients. *A*—normals; *B*—patients with arterial occlusion, but with good collateral circulation; *C*—patients with vasospasm; *D*—patients with deep thrombophlebitis. All pulses are redrawn to the same amplitude and same time duration. Note: the flow to pulse ratios in the patients with arterial occlusion were 2 to 5 times those of the normals.

follows the notch, indicating a larger than normal reflected wave component in the volume pulse (11).

INTERPRETATION OF VASCULAR BEHAVIOR FROM MEASUREMENTS OF FLOW, PRESSURE, AND VASCULAR VOLUME

Flow through a vascular bed is dependent upon arterial pressure, arteriolar inflow and venous outflow resistances, viscosity of the blood, and extravascular pressure. Physiologic control of flow is exerted in many vascular beds by local autoregulation as modified by the influence of autonomic nerves and by circulating constrictor substances.

Analysis of the influences of autonomic nerves and circulating vasoactive substances under conditions of various physiological stresses is complicated, particularly if there is an accompanying change of arterial pressure. For instance, if there is a decrease in arterial pressure to 50 per cent of the control, the measured

peripheral resistance might increase in a nonreactive bed such as the skin, whereas the resistance might decrease in a reactive bed such as that of kidney, brain, or skeletal muscle. These changes would occur in the absence of extrinsic influence. Therefore, in order to analyze the potency of extrinsic influences upon the resistance vessels, it is necessary to obtain previous data on the behavior of the resistance vessels during changes of pressure per se in the absence of extrinsic influences, and then compare the measured changes in resistance with these pre-established findings before drawing any conclusions as to the influence of extrinsic factors on the vascular bed.

Similar observations apply to measurements of vascular volume. The latter measurements become important, particularly in conditions such as shock in which it is presumed that there is a stagnation and pooling of blood in various vascular beds; however, extensive data are not as yet available on such changes in vascular volume.

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Exchange of substances through the capillary walls

E. M. LANDIS

J. R. PAPPENHEIMER¹*Harvard Medical School, Boston, Massachusetts*

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I. FILTRATION AND ABSORPTION; GENERAL FORMULATION

"TRANSUDATION OF WATER AND SOLIDS" through the walls of blood vessels was proposed by Bartholin (10) in 1653 to explain the flow of lymph. This suggestion was largely neglected though a somewhat similar process was expressed vaguely by Hales (140) in 1753 as an "insinuation of liquid" into the wall of the intestine in connection with some of his more prolonged perfusion experiments. Ludwig (223) proposed a definite filtration theory in 1861 based largely upon observations made by Noll (263)

¹ Career Investigator, American Heart Association.

in his laboratory in 1850. According to Ludwig: "... the blood which is contained in the vessel tends to equalize, through the porous vessel walls, its pressure and its chemical composition with those of the fluids which lie outside the vessels. If, for example, the contents of the vessels increases, the pressure in the vessels also increases, and immediately a portion of blood passes out into the tissues, driven by a filtration pressure."

But this "filtration pressure" proved unable, by itself, to explain either the control of the volume of lymph flow or the regulation of the constancy of blood volume. Many of Ludwig's earlier experiments supported his belief that this was accomplished by a direct relationship between blood pressure, filtration, and lymph formation, followed by return of this lymph to the blood stream. Elevating venous pressure in portions of the circulation of a whole animal increased lymph flow, as did also elevating arterial pressure in perfused tissues. However, others showed very soon that elevations of blood pressure produced by vasomotor changes did not always produce the predicted increase of filtration. Moreover, little lymph could be obtained from the resting limb; whereas Ludwig's filtration hypothesis required that even resting blood pressure should have produced both filtration and lymph flow.

The problem became temporarily still more obscure after 1880 when Heidenhain began studying the abundant flow of lymph from the thoracic duct which continued even during rest. The actions of his two classes of lymphagogues, coupled with slight but definite inequalities of solute concentrations in plasma and lymph (explained now, in large part, by the Gibbs-Donnan equilibrium) led him to postulate active secretion by the cells of the capillary walls and possibly by the lymphatics (145a). Heidenhain found Ludwig's simple filtration theory adequate for some conditions and quite unable to explain others. On the other hand, Heidenhain's secretion theory was supported by no direct proof. At this point Starling measured the osmotic pressure of the plasma proteins and added absorption to Ludwig's filtration. In 1896, under the title "On the absorption of fluids from the connective tissue spaces," Starling wrote:

"... although the osmotic pressure of the proteids of the plasma is so insignificant, it is of an order of magnitude comparable to that of the capillary pressures; and whereas capillary pressure determines transudation, the osmotic pressure of the proteids of the serum determines absorption." (345)

This hypothesis, despite its attractiveness, did not

find general acceptance for several decades until improved methods were developed for measuring the osmotic pressure of the plasma proteins and also capillary blood pressure. Apparent exceptions to the hypothesis became explicable as investigators learned more about the nature of the capillary wall itself, the hydrostatic pressure of the interstitial fluid, and the osmotic pressure of the proteins in that fluid.

For purposes of summary, and of consecutive, more detailed discussions of each factor, a general relationship can be formulated. It must be emphasized, however, that this formulation is a composite which is based on many overlapping experiments, each of which dealt simultaneously with several of the variables, but not with all.

$$F.M. = k(P_c - \Pi_{pl} - P_{if} + \Pi_{if}) \quad (1.)$$

+ = filtration
- = absorption

F.M. represents fluid movement through the capillary wall, with a plus sign to indicate filtration, and a minus sign to indicate absorption. P_c is capillary blood pressure (hydrostatic); Π_{pl} , the osmotic pressure of the plasma proteins; P_{if} , the pressure in the interstitial fluid compartment (hydrostatic); and Π_{if} , the osmotic pressure of the proteins in the interstitial fluid immediately outside the capillary walls. The proportionality factor, k , has been called a filtration constant or, more appropriately, a filtration coefficient and is a measure of the permeability of the capillary wall to isotonic fluid. Each of these factors will be considered in succession.

2. CAPILLARY BLOOD PRESSURE, P_c

A. Methods of Measurement

The pressure under which blood flows through the capillary vessels was very much in the minds of the earliest investigators even when pressure measurements were limited to large blood vessels and to lower animals. Thus Hales, in 1773, having determined the first arterial and venous pressures, went on at once to make certain assumptions and then calculated the "force of the blood in the capillary vessels" to be 1.838 gr. with the qualification that to this "must be added the velocity which the blood has acquired at its first entrance in the capillary vessel, which can be but small as appeared by the great resistance it meets within the capillary vessels..." (140). In 1828 Poiseuille (286) devised the U-tube mercury manometer and measured the gradient of pressure

in the arterial system. With smaller and smaller cannulae he measured pressures in the aorta, carotid artery, and even in a 2-mm branch of the crural artery, and reported: "that a molecule of blood moved with the same force throughout the course of the arterial system, which a priori, with all physiologists, we were far from thinking." It followed, therefore, that the major fall of blood pressure must occur somewhere in the smaller vessels beyond the ones he cannulated. Poiseuille then turned his attention to capillary tubes and studied the relation which volume flow of liquids per unit time bears to pressure, viscosity, tube radius, tube length, and wall surface (287-289). Hence Poiseuille's equation, which underlies the science of hydrodynamics, emerged from questions concerning arterial and capillary blood pressure in animals.

In 1875 von Kries (182) tried to measure capillary blood pressure in man by an indirect method. He placed a glass plate, 2 to 5 mm² in area, on the skin and hung from this plate a small scale pan on which weights were placed until the skin blanched. Five years later Roy & Brown (309) used a capsule fitted with a distensible, transparent membrane to determine, under the microscope, the pressures required to modify or obstruct flows through single arterioles, capillaries, and venules in the more or less transparent tissues of experimental animals, e.g., the web of the frog. From 1886 to the present, various modifications of these two basic methods were used for many measurements but yielded discordant results, ranging even in one species, man, and in one tissue, skin, from 1 to 71 mm Hg (207). Most of these studies were made after 1900 because figures for capillary blood pressure were necessary to prove or disprove Starling's filtration-absorption hypothesis. Even as late as 1925 no conclusions could be reached because the lower values were less than venous pressure and obviously questionable.

The higher values were criticized because they were based on blanching of the skin or on arrest of blood flow by microscopic examination, and so indicated arteriolar rather than capillary pressure. Moreover, no indirect method could yield information concerning the presence or absence of a gradient of pressure in the capillary network itself. When reviewed in 1934 (207) indirect methods were found inadequate *a)* because of variable transmission of pressure through overlying tissues to the capillaries beneath, and *b)* because of the arbitrary and unproved criteria adopted by various investigators to indicate when externally applied pressure equaled the pressure

within the capillaries. Direct measurements of the sort attempted by Poiseuille a century earlier were still necessary.

The requirements for direct measurements of pressure in single capillaries are basically simple, though technically somewhat difficult (198, 203). Figure 2.1 shows (upper left) a micropipette, 5 μ in diameter at its tip, under the microscope and ready for use. A somewhat smaller pipette (lower left) is shown inserted into a capillary of the frog's mesentery. The micropipettes are first carefully filled with a saline solution containing heparin, mounted in a micromanipulator and connected to a manometer and syringe (right) so that the pressure exerted on the saline at the tip of the micropipette can be changed rapidly and accurately to balance the changing pressure in the capillary. The micromanipulator is required not only to insert the pipette into the capillary, but also to keep the lumen of the pipette in free communication with the lumen of the capillary. Minute rods (fig. 2.1, upper left), each controlled by its own micromanipulator, are frequently necessary in addition to hold steady thin tissues such as mesentery. Pressure readings from the manometer can be made only at true pressure equilibrium without net flow of liquid through the tip of the pipette because orifices of 5 to 10 μ interpose considerable resistance to flow and consequent inaccuracies. Failure to observe this precaution has yielded fallaciously low values for capillary pressure (36, 203).

With these requirements in mind, suitable criteria were developed for measuring mean, systolic, and diastolic pressures in single capillaries, arterioles, or venules in mesentery (198), skin (205), and muscle of lower animals as well as in the skin of man (203) with an accuracy of a few millimeters of water. Tests showed that changes of capillary pressure induced by graded venous congestion could be detected promptly and accurately by the direct method (203) but not by an indirect method (88).

B. Capillary Pressures in Various Tissues; Relation to the Osmotic Pressure of the Plasma Proteins

Direct measurements of pressures in single capillaries, arterioles, and venules provided answers to Poiseuille's questions concerning the nature and the location of the pressure gradient in the circulatory system. Figure 2.2 shows that in the mesenteric blood vessels of the frog, the major decrease of pressure (70 to 80%) occurred in the arterioles, but there

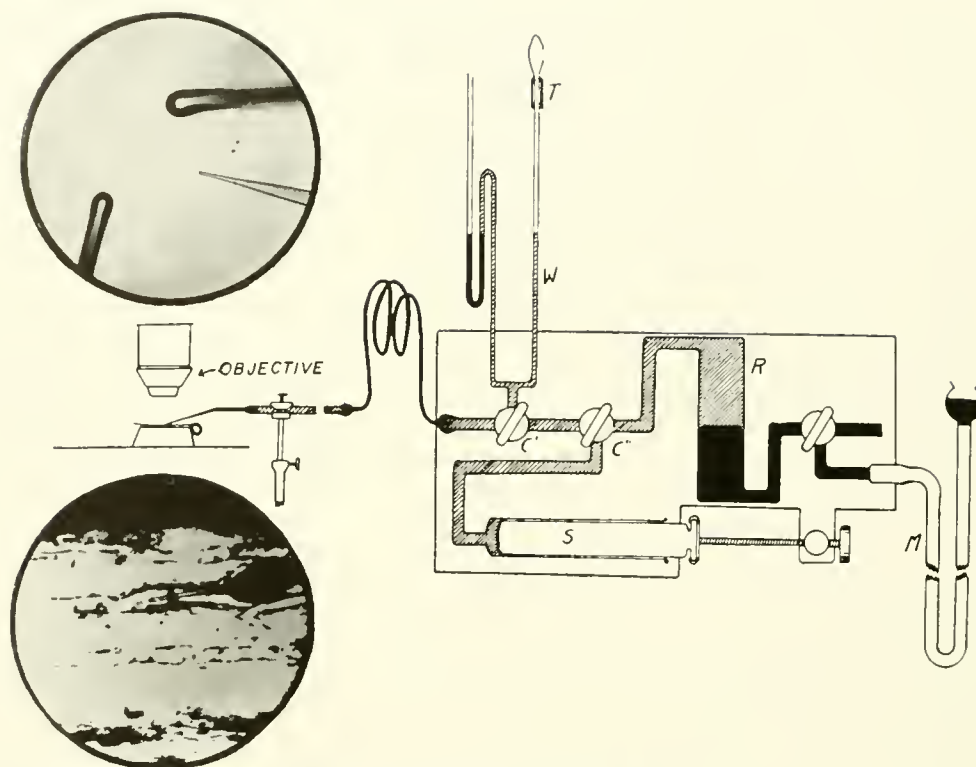
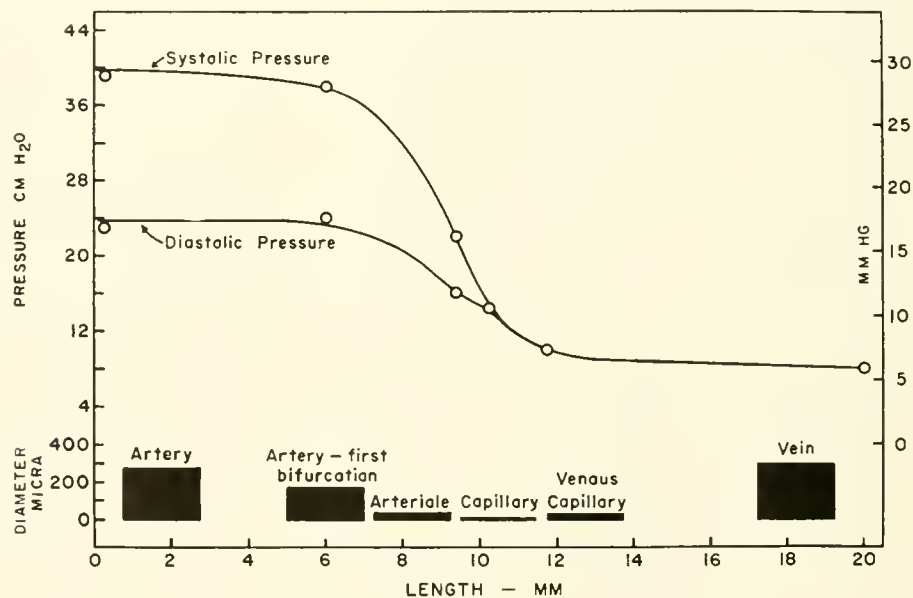


FIG. 2.1. Diagram of apparatus for measuring capillary blood pressure directly. Micro-pipette shown before introduction (*upper left*) and in capillary after introduction (*lower left*). [From Landis (198).]

FIG. 2.2. Curve showing average gradient of pressure through the mesenteric blood vessels of the frog. [From Landis (198).]



was also a significant drop in the capillaries, amounting on the average, with ordinary blood flows, to 20 or 30 per cent of the total (198). A somewhat smaller gradient was also calculated from Poiseuille's equa-

tion and motion picture analyses of flow through capillary networks (206).

The same determinations provided direct support for the Starling filtration-absorption hypothesis.

TABLE 2.1. *Resting Average Capillary Blood Pressure (P_c)* and Osmotic Pressure of Plasma Proteins (Π_{pl})*

| Animal | Π_{pl} | Average P_c | | Tissue (and Reference for P_c) |
|-----------------|------------|----------------|------------|-----------------------------------|
| | | Arteriolar end | Venous end | |
| | mm Hg | mm Hg | mm Hg | |
| Frog | 5-10 | 10.6 | 7.4 | Mesentery (198) |
| | | 11.0 | 7.0 | Muscle (205) |
| | | 10.7 | 7.4 | Skin (205) |
| Rat | 16-21 | 22.1 | 12.5 | Mesentery (202) |
| Guinea pig | 17-21 | 28.3 | 12.5 | Mesentery (202) |
| Cat | 19-26 | 31.3 | 26.8 | Intestine (178) |
| Man | 21-29 | 32.0 | 20† | Skin (203) |
| | | 34.3 | 12.2 | Skin (92) |
| | | 30.6 | 29.5† | Skin (89) |
| | | — | 22† | Skin (225) |
| Man, avg values | 25 | 32 | 24† | 15 |

* Direct measurements only. † Summit of the capillary loop.

In the arteriolar end of the frog's mesenteric capillary network pressure averaged 14.5 cm H₂O or 10.6 mm Hg; in the venous end about 10 cm H₂O or 7 mm Hg. Since the osmotic pressure of the plasma proteins ranged in normal frogs from 5 to 10 mm Hg (41), the approximate balance predicated by Starling was present except when starvation, as in winter frogs, reduced the concentration of plasma proteins (23, 41). As shown in table 2.1, capillary blood pressures in frog's muscle and skin were similar to those in the mesentery (205). In the mesenteries of rats and guinea pigs a balance was also found but at a higher level of pressure (202). Pressures were highest in the intestinal capillaries of the cat (178) and in the cutaneous capillaries of man (89, 92, 203, 225), but again in balance with the higher osmotic pressure of the plasma proteins as shown in figure 2.3. Thus in four tissues and in five species the pressures found were generally compatible with Starling's view that, on the average and at resting blood flows, these pressures favor filtration in the arteriolar portion of the capillary network and a balancing absorption in the venous end of the capillary network. But generalizations cannot be extended to tissues with specialized functions. Capillary blood pressures may be higher in kidney and lower in lung.

Hayman (145) found that glomerular capillary

pressure in the frog averaged 54 per cent of the simultaneously measured aortic blood pressure. White (377) observed pressures of similar magnitude in *Necturus*. For mammalian glomeruli direct measurements are lacking, but indirect estimates have ranged from two-thirds of arterial pressure by Winton (384) to about 50 per cent of arterial pressure by Gottschalk & Mylle (124). The high rate of glomerular filtration can be explained by these high capillary pressures and the greater effective pore area of the glomerular membranes (278). The mechanism by which 98 per cent or more of this filtrate passes back into the blood of the peritubular capillaries cannot be explained so simply.

Postglomerular or peritubular capillary pressures have been measured directly by Wirz (385) who reported 17.4 ± 2.6 mm Hg for a small series of rats and by Gottschalk & Mylle (124) who found averages of 20.4 and 14.2 mm Hg for large and small peritubular capillaries, respectively, under normal conditions. These pressures increased, however, to very high levels not only during venous

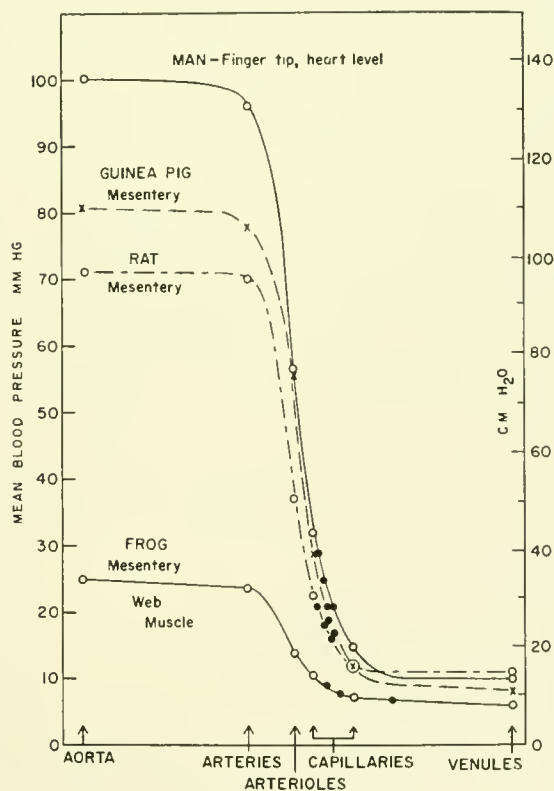


FIG. 2.3. Curves comparing gradient of pressure drop (open circles) in four species with the corresponding osmotic pressures (filled circles) of their plasma proteins. [Modified from Landis (207).]

congestion, but also after dextrose infusions, e.g., to 37 mm Hg, and during ureteral occlusion, e.g., to 40 mm Hg, with relatively close parallelism between intratubular, interstitial, and peritubular capillary pressures. Evidently, the hydrostatic pressure difference across the walls of renal peritubular capillaries is far less than across the walls of peripheral capillaries generally. This implies that the full osmotic force of the plasma proteins, unopposed by hydrostatic pressure differences, may be available for withdrawal of tubular reabsorbate from renal interstitial fluid to blood.

Pulmonary capillary pressure presents an exception in the opposite direction. Though direct measurements are not available as yet, an indirect "wedging" method (146, 147) has made it clear that in the lung capillary pressure is normally between 5 and 15 mm Hg in dog and man and is, therefore, well below the osmotic pressure of the plasma proteins. Absorption is favored (55) and ensures a minimum of interstitial fluid in the alveolar walls, which is an important consideration in a tissue the prime function of which is to permit rapid exchange of gases. In normal subjects these "wedge pressures" are quite constant; exercise produces elevations of not more than 3 or 4 mm Hg. Greater elevations than this during exercise have been found to be helpful in detecting early left ventricular failure or slight mitral stenosis not yet severe enough to produce clinical symptoms or signs (291).

Retinal capillary pressure has not been measured directly, but must be considerably higher than that in muscle or skin in order to maintain blood flow despite an intraocular pressure of about 20 mm Hg. Nor are any reliable figures available for capillary pressures in other special regions, e.g., brain, pleural and peritoneal surfaces, joints, etc. In view of the differences between capillary pressures in skin, kidney, and lung, generalizations are obviously unjustified and direct measurements are needed for each tissue.

C. Variability of Capillary Blood Pressures Under Control Conditions

The average figures so far given would, by themselves, present an erroneous idea of the potential role of capillary pressure in the filtration and absorption of fluid. In any one tissue capillary pressure, like the more easily observed capillary blood flow, varies from moment to moment and from capillary to capillary even when they arise from the same

arteriole. This is to be expected from the responsiveness of the terminal arterioles and arteriocapillary sphincters to nerve impulses, both constrictor and dilator, to local metabolic products and also to mild injury such as that produced by manipulation, exposure to air, and cannulation itself (198, 203, 205). In the skin of frog (205) and man (203) the mere introduction of a minute pipette sometimes produces a brief rise of capillary pressure accompanying the transient vasodilatation of a "triple response" to injury.

It must also be emphasized that capillary pressure has been measured directly in relatively few tissues. In man, determinations have been limited to the capillary loops in the nailfold where arteriovenous anastomoses are also present and may influence pressure measurements. As shown in table 2.1, in one series pressure in the arteriolar loops averaged 32 mm Hg. However, the single readings ranged from 21 to 48 mm Hg; in the venous loops the corresponding figures were 12 and from 6 to 18 (203). In another series of control measurements Eichna & Bordley (89) found even larger variations, much more overlapping of values, and a smaller average gradient, viz. 31 to 22 mm Hg rather than 32 to 12 (table 2.1). These differences may possibly be related to room temperature because the larger gradient and lower pressures in the venous limbs of the capillaries were found at room temperatures of 18 to 20 C (203). The smaller gradient and higher venous capillary pressures were observed in a warm room where temperatures were 23 to 28 C (89). It seems likely that capillary pressures in human digital skin, particularly in the venous limbs next to the subpapillary venous plexus, can be influenced by the state of the arteriovenous anastomoses. At higher room temperatures opening of these large channels, and increased blood flow direct from larger arterioles to larger venules, may well increase pressure locally in the subpapillary plexus into which the true capillaries also discharge their blood.

Chambers & Zweifach (37) have suggested, in addition, a division of function in the minute vessels, viz. that higher pressures, and hence filtration, may occur chiefly in the direct, arteriovenous channels, with lower pressures and absorption located in the true capillaries. For such specialization, however, no supporting evidence in the form of pressure measurements in direct channels is available. Moreover, very high pressures and filtration rates were frequently found in true capillaries (200). Zweifach (387) also suggested that "the arrangement whereby

the true capillaries come off at right angles to the A-V vessels favors the development of 'suction forces,' especially where a rapid, continuous flow courses only through the A-V channels." No suction forces were encountered in any of the many direct measurements of capillary pressure. The reason for this becomes clear in considering actual rather than apparent velocities of flow in the minute vessels. Under the microscope, which magnifies linear velocity as well as size, flows that seem very rapid indeed are really between 1 and 2 mm per sec. Calculation of the magnitude of the corresponding velocity effect by the Bernoulli equation shows the insignificance of any possible suction force, viz. for a linear velocity of 2 mm per sec a pressure difference of only .000015 mm Hg.

Far more important is the conspicuous variability of pressures found throughout the entire minute vessel system as shown in figure 2.4 for the exposed frog's mesentery where measurements could include larger vessels as well as capillaries. In general, high capillary pressures were associated with very rapid flows (if venous outflow was normally free) and with increased pulse pressure in the capillary network. Lower pressures, approaching venous pressure, were associated with slower flow or absence of flow (198). Hence, as arteriolar diameter or tone of precapillary sphincters changes from moment to moment, even under resting or control conditions, the average balance between highly variable capillary pressures and the much less variable osmotic pressure of the plasma proteins often includes temporary imbalances in single capillaries and corresponding shifts toward periods of filtration or absorption. McMaster (235) has suggested that such shifts ex-

plain, in part, the intermittent entry of Locke's solution at atmospheric pressure into the skin through a fine needle introduced carefully to avoid both blood vessels and lymphatics.

Position of a capillary bed, relative to the heart, affects capillary blood pressure in general accordance with changes of hydrostatic pressure (203). In the finger tip of man at heart level average pressure in the arteriolar portion of the capillary loop was 32 mm Hg and in the venous portion 12 mm Hg, with large individual variations in single capillaries around these averages. When the hand was 30 cm above heart level these average pressures became 23 and 10 mm Hg, respectively, further drop being arrested presumably because of collapse of the thin-walled veins in the arm. Conversely, lowering the forearm to 40 cm below heart level increased average arteriolar and venous capillary pressure to 45 and 33 mm Hg, respectively.

The relation between capillary blood pressure and the osmotic pressure of the plasma proteins is therefore extremely labile, both as to time and the area of capillary wall involved. Absorption may be favored in a large segment of the capillary bed for considerable periods, e.g., during vasoconstriction or elevation of an extremity and filtration favored for other periods, e.g., during vasodilatation or dependency. Nevertheless, a net equilibrium is maintained and favors constancy of plasma volume and interstitial fluid volume. Under exceptional conditions, e.g., muscular activity, prolonged dependency of an extremity, high temperature, injury, and inflammation, excessive capillary filtrate must be returned to the blood stream by the lymphatic vessels. These ancillary vessels, as described in the following section,

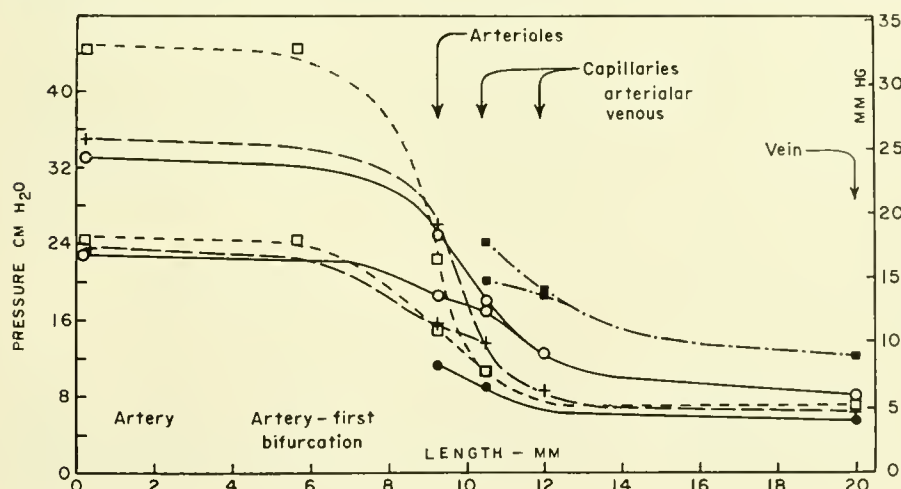


FIG. 2.4. Chart showing variability of capillary blood pressure and of pressure gradient in the blood vessels of the frog's mesentery. The higher capillary pressures and increased capillary pulse pressure are characteristic of vasodilatation. The lower capillary pressures and absence of measurable pulse pressure are characteristic of vasoconstriction. [From Landis (198).]

provide an important safeguard against abnormal accumulations of capillary filtrate in the interstitial fluid compartment.

D. Functional Changes of Capillary Blood Pressure

Hemorrhage and local application of epinephrine produced vasoconstriction in the frog's mesentery and reduced capillary blood pressure as shown in the lowermost curves of figure 2.4 (198). In man the marked vasoconstriction and cessation of blood flow found in Raynaud's disease reduced capillary blood pressure in the affected digits to between 5 and 8 mm Hg, i.e., to levels approaching local venous pressure (204). During the hyperemia of recovery, pressures in these same capillary loops rose rapidly to between 32 and 45 mm Hg. In normal subjects, however, local cooling and vasoconstriction reduced capillary blood pressure only moderately and the rise of pressure during the secondary hyperemia of cold was likewise moderate (203). Also in man Eichna & Wilkins (90) found that neurogenically induced vasoconstriction reduced cutaneous capillary pressure by 1 to 8 mm Hg in 52 of 89 observations with no change or slight elevations of 1 or 2 mm Hg in the remainder. Intravenous injection of 1 or 2 μ g of epinephrine reduced capillary pressure by 1.5 to 22 mm Hg in seven of ten experiments but in three subjects elevations of 1 or 2 mm Hg were observed. Sympathectomy obliterated neurogenic effects, but not those of epinephrine. In the vasoconstriction of human hypertension capillary pressure was not significantly elevated and minor increases found in some subjects were independent of arterial pressure (89); this was also true of the temporary rise of arterial pressure produced by Paredrinol intravenously (87) with or without prior sympathectomy.

Conversely, vasodilatation increased capillary blood pressure, frequently to very high levels approaching arteriolar pressure (see fig. 2.4). Capillary pressure also rose during local vasodilatation induced in the frog by dilute urethan (198), by injuries which produced hyperemia and capillary stasis (199), by a simple triple response and after muscular contraction (205). In human skin the hyperemias of local heating, intradermal histamine, inflammation, and reactive hyperemia after cold (203) were accompanied by elevations of capillary pressure to maxima between 49 and 60 mm Hg. In these observations room temperatures were low, 18 to 20 C. At higher temperatures, 23 to 28 C, Eichna & Bordley (89) found that intradermal histamine

elevated capillary pressures much less conspicuously and more in the venous than in the arteriolar limbs in both normal and hypertensive subjects. It was emphasized that arteriovenous anastomoses may have been involved in these effects (203).

From the higher capillary pressures found in localized vasodilatation and hyperemia it might be thought that excessive filtration and increased lymph flow must occur with any vasodilatation. This is not always the case, however. The most notable exception is the repeated finding that denervation of an extremity produces hyperemia and evidence of increased blood flow without change of lymph flow, or at most a very slight increase, as reviewed by Drinker & Field (76). This failure of widespread vasodilatation to increase the flow of lymph was, in fact, for many years cited as evidence against the Starling hypothesis. Eichna & Bordley (89) found that reactive hyperemia and also indirect or reflex vasodilatation in man, produced by body warming, did not increase cutaneous capillary pressure significantly. The reason for this may lie in the lowering of pressures in the digital arteries by 10 to 40 mm Hg during the generalized vasodilatation produced by body warming (73, 114, 115, 244), by exercising the forearm muscles (73), or by reactive hyperemia (365). The named arteries to an extremity are apparently large enough to conduct blood at resting flow rates with little pressure drop. The lesser increments of flow required by localized vasodilatation are associated with little drop in arterial pressure and capillary pressure rises conspicuously. However, when vasodilatation involves the resistance vessels of a whole extremity, and blood flow through the large arteries is increased severalfold, the pressure drop from brachial artery to digital artery becomes significant. Then, arterial pressure head being much reduced locally, the rise of capillary pressure is limited even with maximal arteriolar dilatation. In addition, the capillaries lie between two resistances and it is quite possible that arteriolar dilatation will not raise capillary pressure if the venules and veins are simultaneously dilated in similar or greater proportion.

E. Effects of Venous Pressures and of Venular Constriction on Capillary Pressure

Elevations of venous pressure produce, as might be expected, a rapid increase of capillary pressure to levels above the pressure in the veins. Direct measurements have shown this to be true of localized

obstruction of a venule in the frog's mesentery (198) and also when the human extremity was congested by inflating a cuff previously placed on the upper arm (88, 203). When blood flow was normal, capillary pressure equalled cuff (and venous) pressure within 15 to 45 sec and eventually exceeded cuff (and venous) pressure by 8 to 14 mm Hg in the 2nd to 4th minute of congestion (203). When blood flow was very slow, however, as in the arteriolar constriction of acrocyanosis (220), capillary pressure rose much more slowly, requiring up to 8 min to equal venous pressure and finally exceeding that pressure by only 1 or 2 mm Hg. Other direct measurements have shown that capillary pressure is elevated in congestive heart failure (92) and also in glomerulonephritis (225) whenever venous pressure is high, returning to normal as venous pressure declines. In all these measurements the variability of normal, resting capillary pressures prevents making any meaningful comparison of the increment of capillary pressure which corresponds to any given increment of venous pressure.

The effect of venous pressure on capillary pressure was emphasized in 1894 on the basis of indirect evidence by Bayliss & Starling (12) when they observed that elevating venous pressure increased lymph flow more than similar changes of arterial pressure. In the absence of a direct method of measuring capillary pressure they suggested using changes of venous pressure to deduce changes of capillary blood pressure. Also, from studies of lymph formation, Drinker & Field (76) in 1933 suggested that, other things remaining constant, the state of the veins might modify capillary pressure and thereby influence filtration of fluid through the capillary wall. In 1948 Pappenheimer & Soto-Rivera (282) found in the denervated, perfused extremities of cats and dogs that a given change of venous pressure influenced filtration and absorption five to ten times more than did a similar change of arterial pressure. They formulated the dependence of mean capillary pressure on arterial and venous pressures and resistances as follows:

$$P_C = \frac{\frac{r_v}{r_a} p_A + p_v}{1 + \frac{r_v}{r_a}} \quad (2.1)$$

in which r_v and r_a are, respectively, the precapillary and postcapillary resistances, while p_A and p_v are, respectively, arterial and venous pressures. From this equation it follows that at given values of arterial

and venous pressures the mean capillary pressure depends on the ratio of the postcapillary to precapillary resistance to blood flow. Contractility of the large veins has been well established for a long time, but even in 1950 a general review (210) revealed little information concerning reactions of small veins or venules and only a few instances of independence of such reactions from those of the arterioles.

Beginning in 1954 Haddy *et al.* (137) approached the question of differential changes in precapillary and postcapillary resistances by threading catheters, outside diameter 0.2 to 0.5 mm, as far as possible into "small veins" and "small arteries" for measurement of pressures. Under control conditions small artery pressures averaged 65 ± 25 mm Hg, while small vein pressures, under local anesthesia, averaged 13 mm Hg with a range of 8 to 25 mm. Small vein pressure varied independently of the relatively constant large vein pressure, indicating that the small vein system must be responding independently to nervous or humoral stimuli. Kelly & Visscher (171) found that independent pressure changes in small arteries and small veins were produced by stimulating the lumbar sympathetic chain in dogs. Variability of these changes in timing, magnitude, and even direction was considerable and three main types or combinations of pressure changes had to be described. In further studies small vein pressure increased to as much as 36 mm Hg and led to the suggestion by Lee & Visscher (214) that edema of the skin could have a neural origin. However, were this an important possibility one would expect that cutaneous edema would be observed at some stage in the progressive, neural vasoconstriction found in hemorrhage and shock. This is, however, not the case. It must be remembered, too, that if arterial pressure remains constant, or especially if it falls, any constriction, whether arteriolar or venous, tends to reduce blood flow and this then tends to limit edema formation to the extent that renewed volumes of blood plasma are not available for filtration; at zero blood flow even the wheal of histamine does not appear (216, 217, 219).

Extending this method to humoral agents, Haddy and others found that independent, and sometimes opposite, reactions of arteries, small arteries, small veins, and large veins were produced by change of tissue temperature (135, 364), change of pH (105), epinephrine (134), norepinephrine (134, 364), serotonin (134, 136) and histamine (133). As summarized by Haddy *et al.* (134), "almost every possible combination of active and passive change in seg-

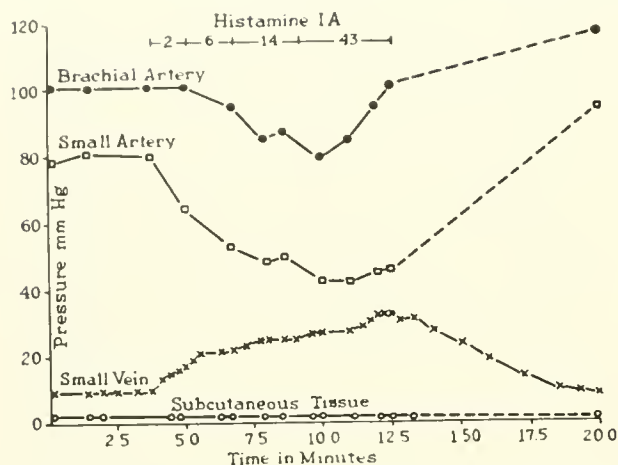


FIG. 2.5. Effect of histamine infused intra-arterially upon vascular and interstitial pressures in the dog's foreleg. Numbers at top refer to $\mu\text{g}/\text{min}$ histamine base administered into the brachial artery. [From Haddy (133).]

mental resistances and pressures has been observed during one or another arrangement." The true significance of these findings is correspondingly difficult to evaluate. In the case of histamine (fig. 2.5), which has been more thoroughly studied at controlled flow rates, this elevation was ascribed for small doses simply to arteriolar dilatation, and for large doses to an added selective constriction of small veins. This constriction in turn was ascribed in part to the direct action of histamine and in part to indirect effects stemming from release of norepinephrine from the adrenal medulla. It was suggested also that the resulting changes of capillary pressure might be sufficient to explain the protein-rich edema, produced by histamine, on hydrostatic grounds by passive congestion, increased capillary pressure and stretching of the capillary wall, without invoking injury of the wall by histamine. The production of a protein-poor filtrate is certainly possible, but the production of a protein-rich filtrate seems unlikely. The small vein pressures reported were all below 40 mm Hg, whereas it has been shown, with venous pressures of 40 to 60 mm Hg, that capillary filtrate contained at most 0.7 g per cent of protein and averaged only 0.3 g per cent (211), not the 4 or 5 g per cent found in the histamine wheal (217).

The validity of conclusions based on such catheterization of small veins is doubtful for several reasons. In addition to inescapable, even though slight, obstruction to venous outflow and false elevations of "small vein pressure" there is the possibility of effects from trauma to the intima of the venules under study. Davis & Hamilton (65-67) stimulated the

sympathetic nerves to the rabbit's ear and the dog's paw and found that the pressures developed in the small veins depended upon the nerve stimulated, upon the frequency of stimulation, upon the rate of blood flow, and upon the presence or absence of mechanical obstruction to venous outflow. They found also that the highest small vein pressures occurred while flow in the region had stopped. Pressures in the small veins sometimes exceeded those in the small arteries (fig. 2.6, right). They concluded that when this occurred the walls of the small veins were constricting against a static column of blood isolated probably from the capillaries, and certainly from the arterioles. Burch (29) observed similar elevations of pressure in isolated segments of large veins in man.

More recently still, an isovolumetric technique has been used by Mellander (243) to measure the effects of sympathetic stimulation on the resistance and capacitance vessels in cats with hind legs placed in a plethysmograph. As shown in figure 2.7, frequency of stimulation was kept within physiological limits, i.e., from 0.25 to 16 stimuli per sec. Both the capacitance vessels and resistance vessels constricted. The former responded more actively at first and reached maximum constriction at 8 stimuli per sec. The resistance vessels were influenced less at low stimulation rates and more at higher rates. Precapillary resistance increased more than postcapillary resistance and increasing absorption was found, with calculated reductions of capillary blood pressure ranging from 2 to 15 mm Hg. Mellander suggested that Kelly and Visscher, by manipulating and cannulating the small veins, may have produced local constriction of their walls. In addition to the obstruction already mentioned, it is also possible that intimal irritation, secondary to catheterization or cannulation, may make the small veins abnormally susceptible to vasoconstrictor impulses. In any event it seems clear that, under some conditions, stimulation of sympathetic vasoconstrictor nerves increases arteriolar resistance more than venous resistance, reduces capillary blood pressure, and leads to rapid and significant absorption of fluid and not to elevated capillary pressure and filtration.

By the same technique Mellander showed that epinephrine in small doses, and in muscle, relaxed the arterioles and probably constricted the venules slightly, producing filtration and hence indirect evidence of a rise of capillary blood pressure. In skin, all doses, and in muscle large doses of epinephrine produced effects like those of sympathetic stimulation, but only 20 to 25 per cent as great. Norepi-

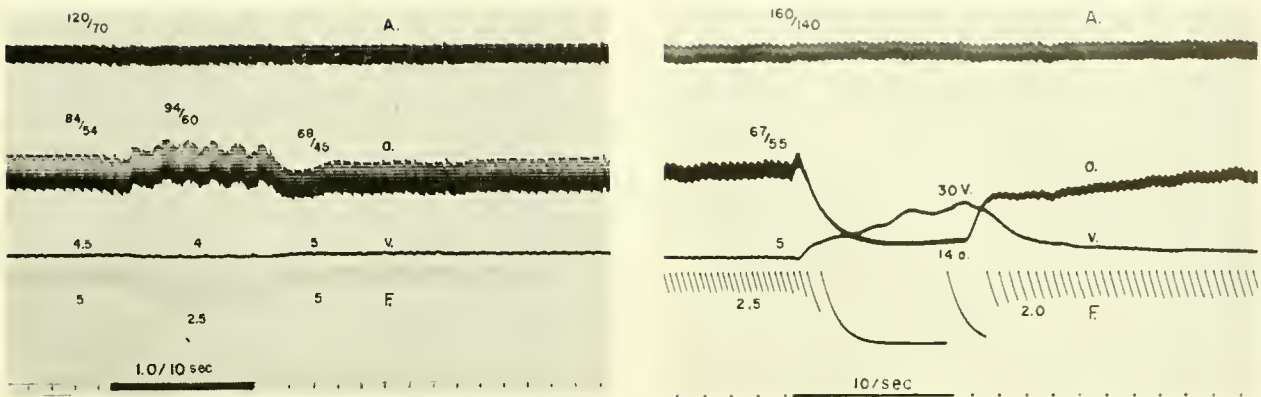


FIG. 2.6. *Left:* small vessel pressure and flow response to a low-frequency stimulation of the ipsilateral lumbar sympathetic trunk (15 v, 1 stimulation/10 sec for 1 min) Aortic pressure (A), small artery pressure (a), small vein pressure (v), and small vein flow (F) against atmospheric pressure. Numerals on pressure tracings indicate pressure in mm Hg. Numerals on flow tracing represent flow in ml/min. Timer set at 10 sec. *Right:* same but with high frequency stimulation (15 v, 10 stimulations/sec for 1 min). Symbols same except that F is small artery flow proximal to distal segment. [From Davis & Hamilton (66).]

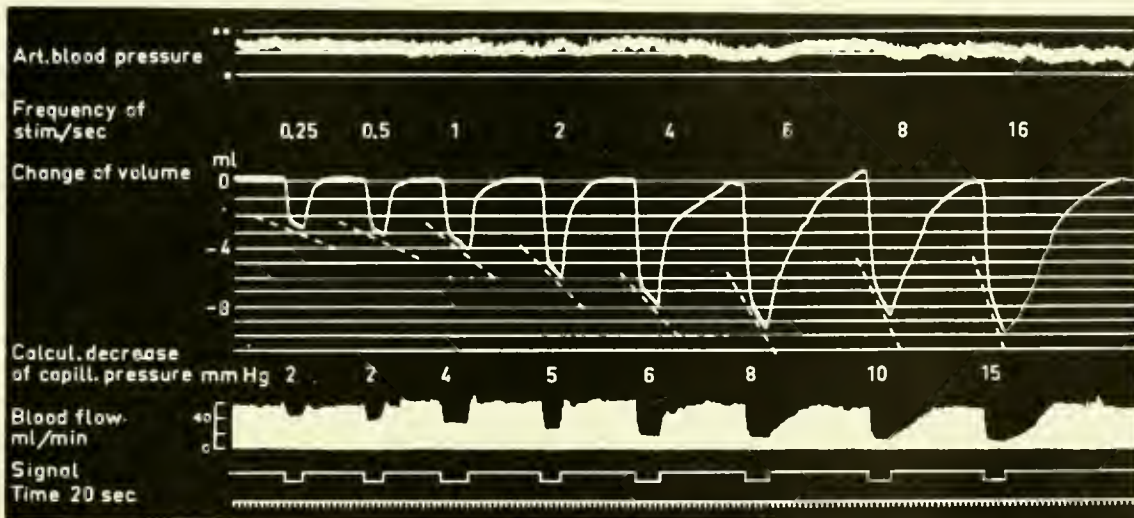


FIG. 2.7. Effects on resistance and capacitance vessels and net transcapillary fluid shift produced by maximal lumbar vasoconstrictor fiber stimulation at different frequencies. Changes in blood flow reflect effects on resistance vessels (inflow and outflow pressures kept constant). The initial and rapid decreases in volume reflect effects on capacitance vessels and the subsequent slower and continuous decreases in volume (slopes indicated by dashed lines), transcapillary influx of extravascular fluid. Reductions in mean hydrostatic capillary pressure calculated in approximate figures. [From Mellander (243).]

nephrene was also constrictor and produced absorption of fluid. Acetylcholine increased blood flow markedly but produced less filtration than small doses of epinephrine. Presumably capillary pressure increased very little because pre- and postcapillary resistances were reduced equally. Johnson and Hanson (168a) have recently applied the isogravimetric technique

to a study of pre- and postcapillary resistance in the intestine of the dog. In this preparation, the isogravimetric capillary pressure is only about 65 per cent of the plasma protein osmotic pressure, probably reflecting the higher permeability to protein of intestinal capillaries. The postcapillary resistance to blood flow through the intestine was increased markedly when

arterial perfusion pressure was decreased and evidence was presented that this reaction depends upon sympathetic innervation of the postcapillary blood vessels (142a).

One more series of studies must be mentioned briefly because the possible role of the arteriovenous anastomoses on small vein pressures has not been mentioned so far. These relatively large vessels run parallel to the capillaries and are numerous in the skin, particularly of the digits. Schroeder (324), using a pressure plethysmograph similar to that used in man by McLennan *et al.* (234), studied the effects of acetylcholine, epinephrine, histamine (325), hypoxia (327), calcium, and rutin (326) on vascular volumes and pressures in the dog's foreleg. External pressure was set arbitrarily at 35 mm Hg to measure "changes of capillary pressure" and at 15 mm Hg to measure "changes of venous pressure." No absolute pressure readings could be obtained by this method. The curves were variable and often difficult to interpret. However, Schroeder placed considerable emphasis upon independent reactions of the arteriovenous anastomoses and their secondary effects upon venous and capillary pressures. It is conceivable that some of the variability in the observed small vein pressures in the skin of the extremities may be reduced, or at least explained in part, if body temperature and environmental temperatures are adjusted to maintain the arteriovenous anastomoses in as constant a state as possible. In any case it is clear that pressures and resistances in large veins and in small veins, together with any factors which modify them, must be taken into account when describing the mechanisms which determine changes of capillary blood pressure.

3. OSMOTIC PRESSURE OF THE PLASMA PROTEINS, Π_{pl}

A. Methods of Measurement

Starling's conception of a balance between capillary hydrostatic pressure and protein osmotic pressure was supported by actual measurement of the pressure required to maintain fluid balance across a semi-permeable membrane separating blood serum from serum ultrafiltrate. Starling's osmometer consisted of a small glass bell, provided at the top with two side arms. A piece of peritoneal membrane, soaked in 10 per cent gelatin, was tied over the mouth of the bell and prevented from bulging by a perforated silver plate. One sidearm was connected to a vertical tube and the other side arm was used to introduce serum into the bell. The lower end of the bell, in-

cluding the membrane, was then dipped into serum ultrafiltrate or other protein-free salt solution. Within a few hours osmotic flow of fluid from the salt solution through the membrane was made evident by a rise of fluid in the vertical tube. Equilibrium was established in 2 to 6 days; at this time the pressure on the membrane, exerted by the fluid column in the vertical tube, was considered equal and opposite to the osmotic pressure of the serum proteins. In a typical measurement Starling (345) found that serum containing 7.56 per cent "proteids" caused fluid to rise in the vertical tube to a height of 53 cm (~ 41 mm Hg). This value is considerably higher than modern estimates shown in figure 3.1, probably as a result of bacterial degradation of protein during the long period required to reach equilibrium. In later work (1899) Starling (347) obtained values which were generally lower than his first estimate and well within the range expected for capillary hydrostatic pressures.

Starling's measurements were of great interest to colloid chemists as well as to physiologists. According to van't Hoff's analogy, in 1887, between ideal solutions and gases (157), the osmotic pressure, Π , should be given by

$$\Pi = cRT \quad (3.1)$$

where c is expressed in moles per liter.

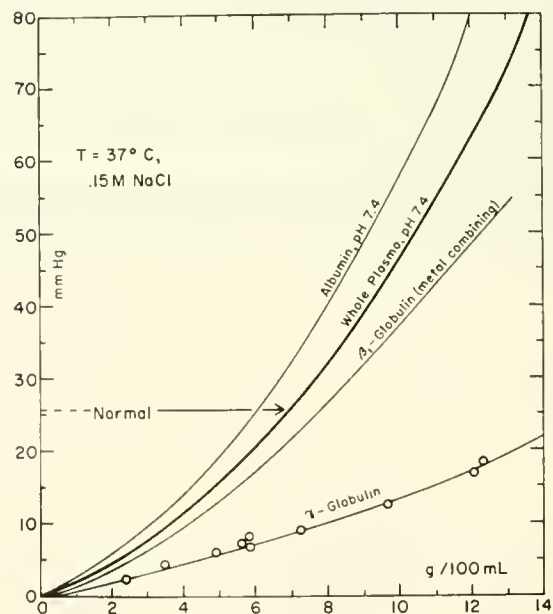


FIG. 3.1. Osmotic pressure-concentration curves for whole plasma and selected plasma proteins. Based on data from references (268, 270, 312, 313, 343), original measurements corrected to 37°C. Experimental points for γ -globulin are included to indicate magnitude of experimental error.

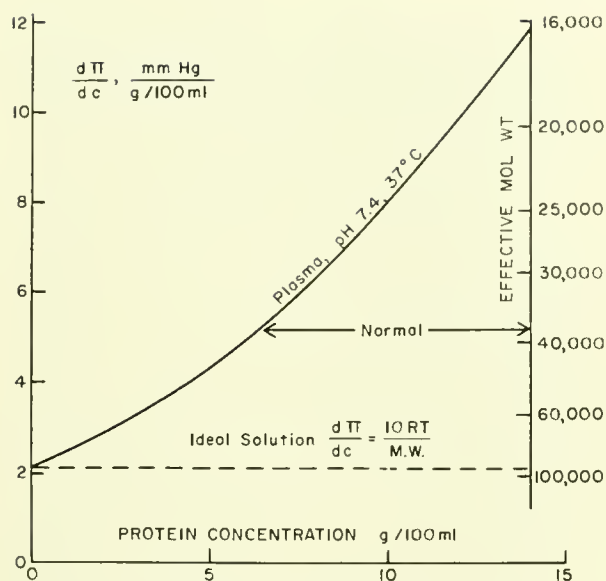


FIG. 3.2. First derivative of protein osmotic pressure-concentration curve to show deviation from van't Hoff's law. At infinite dilution the mean number average molecular weight of plasma proteins is almost 100,000 but in normal plasma their osmotic behavior corresponds to an ideal solute of mol wt 37,000.

If c is expressed in g per 100 ml, RT in liter-atmospheres, and Π in atmospheres, then

$$\text{Mol. Wght.} = 10c \ RT / \Pi \quad (3.2)$$

The potential application of equation 3.2 to the determination of molecular weights led protein chemists to investigate in detail the theory and technique of osmotic measurements. As early as 1905, Reid (293) used Starling's technique to estimate the molecular weight of hemoglobin. Subsequent studies by Sørensen (342), Adair (1, 2), and others showed that protein osmotic pressure is dependent upon ionic strength, net charge, and other factors not included in van't Hoff's limiting law for ideal solutions. Deviations from the limiting law increase rapidly as a function of protein concentration (figs. 3.1 and 3.2) and estimates of molecular weight can only be made on the basis of extrapolation to zero concentration. The chief technical difficulty confronting early workers was the long period required to reach equilibrium across artificial membranes. In order to avoid bacterial degradation of protein it was necessary to carry out measurements at low temperature; days or even weeks were required for each determination. Nevertheless, the first satisfactory estimates of the molecular weights of serum albumin (3), ovalbumin (342), and hemoglobin (2) were obtained by this method.

Advances in the technique of osmometry have reduced considerably the time required for the equilibration process.

Equilibration across a semipermeable membrane, following a step change in either hydrostatic or osmotic pressure, proceeds exponentially with a time constant equal to the product of membrane resistance and volume distensibility

$$\% \text{Equilibrium} = 100 \left[1 - \exp \frac{-t}{r_m(v_p + v_m)} \right] \quad (3.3)$$

where r_m is membrane resistance to solvent flow and v_p , v_m are the volume distensibilities of the pressure measuring device and membrane, respectively. The resistance (r_m) of membranes capable of restraining the passage of serum albumin is seldom less than 10^4 mm Hg per ml per hour per cm^2 membrane. The essential factor limiting the rate of approach to equilibrium is therefore the volume of fluid which must pass through the membrane in order to actuate the pressure detector and satisfy the volume-pressure characteristics of the membrane. For example, a typical osmometer with a membrane surface area of 10 cm^2 must have a total volume distensibility of less than 3×10^{-4} ml per mm Hg in order to achieve 95 per cent equilibrium in 1 hour (equation 3.3).

In 1936 Hepp (151) described an osmometer in which distensibility of the membrane (v_m) was made extremely small, the chief volume displacement being confined to slight changes in fluid level of the capillary tube manometer used to detect pressure balance. Equilibration time was reduced to about 2 hours. Osmometers of the Hepp type have been widely used by subsequent investigators and the osmotic pressure-concentration curves shown in figure 3.1 are based on data obtained with this instrument. A recent description of the construction and use of Hepp osmometers has been published by Meschia (248). Further reduction in volume displacement can be obtained through the use of sensitive, recording pressure transducers having volume distensibilities less than 10^{-6} ml per mm Hg. With the aid of such transducers it is theoretically possible to achieve 95 per cent equilibration across available protein-impermeable membranes in less than 1 min. Recording osmometers of this type, having time constants of less than 5 min, have been in use in the authors' laboratory for several years (277, 280). Similar instruments, suitable for the rapid estimation of protein osmotic pressure in 0.1 ml plasma, have recently been described by Hansen (142).

B. Protein Osmotic Pressure of Human Plasma

Osmotic pressure-concentration curves for normal human plasma, serum albumin, and two globulin components of plasma are shown in figure 3.1. The curves were obtained at physiological pH and ionic strength, but the original measurements have been corrected to 37 C. Experimental points, taken from Oncley *et al.* (268), are shown for γ -globulin in order to indicate the magnitude of experimental error when a pure component is measured. The smooth curves for albumin, whole plasma, and β_1 -globulin are based on data in references (268, 270, 312, 313, 343). Normal human plasma has a

protein osmotic pressure of 24 to 26 mm Hg, corresponding to a total protein concentration of about 7 per cent. It is impossible to give a significant mean value because the protein concentration depends upon procedures used for drawing blood samples and in any given sample the value obtained depends upon the method of measurement. Electrophoretic measurements yield slightly lower values for total protein than estimates based upon salt precipitation or protein nitrogen. In the following discussion a nominal value of 7.0 g per 100 ml will be considered normal.

The osmotic pressure-concentration curves for albumin and for normal plasma are described by the following empirical equations which fit the experimental data closely over the range 0 to 25 per cent protein.

$$\pi \text{ albumin} = 2.8c + 0.18c^2 + 0.012c^3 \quad (3.4)$$

$$\pi \text{ plasma} = 2.1c + 0.16c^2 + 0.009c^3 \quad (3.5)$$

In each equation the first term represents the ideal limiting law of van't Hoff. Thus the molecular weight of albumin, calculated from the first term of equation 3.4, is $10 RT/2.8 = 69,000$. The second and third terms in each equation represent deviations from van't Hoff's law caused by Donnan effects and protein-protein interaction.

The chief osmotically active protein in normal mammalian plasma is albumin, which can be separated and identified as a homogeneous component representing about 50 per cent of the total protein in plasma and contributing about 65 per cent of the protein pressure. The globulins, on the other hand, comprise a spectrum of components with molecular weights ranging from 45,000 to 1,000,000 as shown in table 3.1. The widely different osmotic activities of β_1 -globulin and γ -globulin shown in figure 3.1 serve to emphasize that no simple physicochemical meaning can be attached to the osmotic pressures developed by crude, heterogeneous globulin fractions. Precipitation methods fail to separate albumin from low molecular weight globulins which contribute substantially to total protein osmotic pressure; for this reason many early studies attempting to relate total protein pressure to albumin:globulin ratios (380) need to be reevaluated. Current estimates of A:G ratio in normal plasma are close to 1.1, in comparison with values in the range 1.8 to 2.6 obtained by classical fractionation procedures.

The osmotic pressure contributed by globulins can be calculated from the difference between albumin and whole plasma (equations 3.4, and 3.5),

it being assumed that the A:G ratio is 1.1 and that osmotic interactions between globulins and albumin are not significantly different from interaction between albumin and albumin (270, 314). The "average" globulin curve so calculated is given by

$$\pi \text{ globulins} = 1.6c + 0.15c^2 + 0.006c^3 \quad (3.6)$$

In normal plasma about 15 per cent of the total protein pressure is contributed by known globulin components and about 20 per cent by unidentified components (table 3.1). Bennhold *et al.* (14) have studied two extremely interesting cases of complete analbuminemia; the osmotic pressure-concentration curve of the albumin-free plasma from these unique patients (brother and sister) conforms closely to equation 3.6 (271). These patients have been in good health for many years despite the fact that the protein osmotic pressure of their plasma is less than 50 per cent of normal. Presumably they have compensated by permanent reduction of mean capillary pressure to balance the low protein pressure.

C. Species Differences, Fetal Plasma

Comparative studies of colloid osmotic pressure have been reviewed by Meyer (251) and by Keys & Hill (175). A summary of data pertaining to plasma of Elasmobranchs, Pisces, Amphibia, Reptilia,

TABLE 3.1. *Some Protein Components of Human Plasma**

| Component | Conc. g/100 ml | % of Total Protein | mol wt | Approx. π in Plasma mm Hg |
|------------------------------------------------|----------------------|--------------------------|-----------------|-------------------------------------|
| Whole plasma | 7.0 | 100 | | 25 |
| Albumin | 3.6 | 51 | 69,000 | 16.4 |
| γ -Globulins | .7 | 11 | 156,000 | 0.9 |
| Fibrinogen | .3 | 4 | 340,000 | 0.2 |
| α -Lipoprotein ($1.0 < p < 1.14$) | .28 | 4 | 160-400,000 | 0.2 |
| β -Lipoprotein ($p = 1.03 \pm .02$) | .25 | 3.8 | 2×10^6 | |
| β_1 -Metal combining | .2 | 3 | 90,000 | 0.7 |
| β_2 -Globulins | .2 | 3 | (150,000) | 0.4? |
| β_1 -Lipid poor euglobulin | .13 | 2 | (150,000) | 0.2? |
| α_1 -Acid glycoprotein | .03 | 0.4 | 45,000 | 0.2? |
| Remaining known components | .4 | 5 | | <1.0 |
| Total | 6.0 | 87 | | ca. 20 |
| Unidentified | 1 | 13 | | 5 |

* Prepared with J. L. Oncley; cf also ref. 267.

Aves, and Mammalia will be found in reference (4). It is a striking fact that all mammals have approximately the same protein osmotic pressure. Mean values for the various species of mammals listed by Meyer (251) range from 19 mm Hg (guinea pig) to 26 mm Hg (human), but data from most species lie in the range 21 to 25 mm Hg. These relatively small variations among species may well be spurious. Excitement, posture, anesthesia, and many other factors can cause substantial hemodilution or hemoconcentration prior to withdrawal of blood samples. It would be unjustified to compare blood obtained from a confident, unanesthetized human with blood obtained from animals in various states of excitement and anesthesia.

Protein concentrations and osmotic pressures in plasma of poikilotherms are in general far lower than in mammals. Values in the range of 5 to 10 mm Hg have been reported for frogs and turtles (35, 189, 200), the lower values being associated with the spring season. The low protein osmotic pressure of poikilotherms is to be expected in view of their relatively low blood pressure. It is surprising, however, to find similarly low values in birds in which blood pressure is relatively high.

The protein osmotic pressure of fetal plasma is of special interest in relation to fluid exchanges between maternal and fetal blood. Meschia (249) has carried out a careful series of osmotic measurements in fetuses from sheep and goats. At midterm the protein osmotic pressure in fetal blood is 7 to 10 mm Hg; the pressure gradually increases during gestation but never exceeds that in maternal blood. The average molecular weight of proteins in fetal plasma is only 65,000 as compared with 96,000 in the adult. This difference is largely due to the presence of fetuin (283a), a low molecular weight globulin which accounts for about 90 per cent of the globulin fraction. The mean molecular weight increases dramatically within 24 hours after birth, owing partly to absorption and retention in the blood of γ -globulins from colostrum.

D. Physiological Significance of the Deviations from van't Hoff's Law

The disproportionate increase in protein osmotic pressure as a function of concentration tends to amplify osmotic forces contributing to homeostasis of blood volume. The magnitude of this effect is seldom appreciated and will therefore be discussed in some detail. Figure 3.2 shows the rate of change of

osmotic pressure per unit change in concentration, as a function of concentration. At small protein concentrations, such as those existing in tissue fluids, the osmotic coefficient, $d\Pi/dc$, is relatively small and the proteins behave as the osmotic equivalent of an ideal solute of molecular weight 80,000 to 90,000. Thus the osmotic forces in interstitial fluid tending to withdraw fluid from blood are relatively small and insensitive to quite large percentual alterations in protein concentration. At concentrations which exist in plasma, however, the osmotic coefficient is almost threefold greater so that the plasma proteins behave as the osmotic equivalent of an ideal solute of molecular weight 37,000. If the proteins behaved as ideal solutes they would have to be present in plasma at a concentration of 12 per cent in order to exert the same osmotic pressure. The viscosity of such a concentrated solution would more than double peripheral resistance to blood flow. On the other hand, an ideal solute of molecular weight 37,000 (i.e., osmotically equivalent to the proteins in plasma) would pass rapidly through the capillary walls and therefore be ineffective in balancing capillary hydrostatic pressure.

The functional significance of the nonlinear osmotic properties of the plasma proteins is further illustrated in figure 3.3. Fluid loss from plasma, amounting to

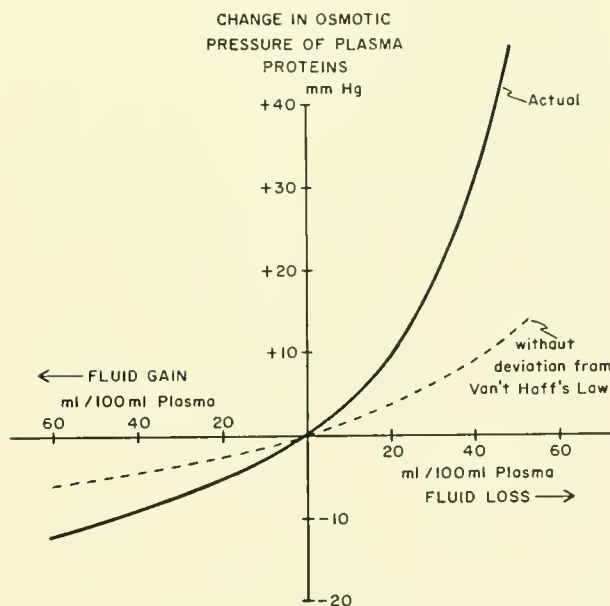


FIG. 3.3. Physiological significance of deviations from van't Hoff's law. Fluid loss from plasma causes a disproportionately large increment in the osmotic restoring force; conversely, hemodilution causes a relatively small diminution of protein osmotic pressure.

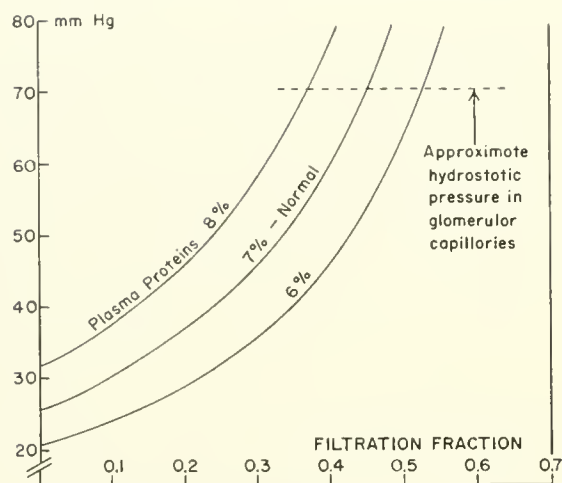


FIG. 3.4. Illustrating the significance of protein osmotic pressure for glomerular filtration. The rapid increase of protein osmotic pressure as a function of concentration places an upper limit to the filtration fraction of the kidney.

30 ml per 100 ml, results in an increase of 18 mm Hg in the osmotic restoring force, resisting further fluid loss. If the plasma proteins behaved as ideal solutes, however, the restoring force would be only 6 mm Hg. Conversely, dilution of the plasma results in a greater reduction of osmotic pressure than would obtain if the proteins behaved as ideal solutes. These considerations are of special importance normally in connection with glomerular filtration where a relatively large fraction of plasma fluid may be filtered. Figure 3.4 shows protein osmotic pressures in efferent glomerular blood as a function of filtration fraction. It is clear that the steep rise of protein osmotic pressure is an important factor limiting filtration rate. For example, a filtration fraction of 0.45 is the highest possible value consistent with a normal plasma protein concentration (ca. 7%) and a normal hydrostatic pressure (ca. 70 mm Hg) in the glomerular capillaries. It is probable also that the high protein osmotic pressure in efferent glomerular blood plays a major role in providing the force for transcapillary absorption of fluid in the peritubular circulation.

E. Physicochemical Aspects of Protein Osmotic Pressure

In the preceding paragraphs we have emphasized the functional significance of the large deviations from van't Hoff's law which characterize osmotic behavior of plasma proteins. It therefore seems appropriate to discuss briefly the physical forces which contribute to nonlinear osmotic behavior of this type.

The disproportionate increase in osmotic pressure as a function of protein concentration (figs. 3.1 and

3.2) can be explained in part by net charges on the protein molecules which cause unequal distribution of electrolytes across the semipermeable membrane (Donnan effect). Combination of van't Hoff's limiting law (equation 3.1) with the ionic distribution required by Donnan equilibrium for univalent ions yields the following relation.

$$\Pi = RT(c + \sqrt{z^2 c^2 + 4m_s^2} - 2m_s) \quad (3.7)$$

where c = protein concentration, moles per liter; z = net charge² on the protein, and m_s = the concentration of salt solution with which the protein is equilibrated. A simple derivation of equation 3.7 may be found in reference (156). A more convenient form of equation 3.7 may be obtained from expansion of the second term by means of the binomial theorem. Thus,

$$\sqrt{z^2 c^2 + 4m_s^2} = 2m_s + \frac{z^2 c^2}{4m_s} - \frac{z^4 c^4}{64m_s^3} + \dots \quad (3.8)$$

The third term of the series is negligible except at very low salt concentrations. Substituting the first two terms of the series in equation 3.7 we obtain the form derived by Scatchard *et al.* (313)

$$\Pi = RT\left(c + \frac{z^2 c^2}{4m_s}\right) \quad (3.9)$$

Equation 3.7 or 3.9 describes qualitatively some of the observed changes in osmotic pressure as a function of protein concentration, charge, and salt concentration. Thus osmotic pressure is increased when the salt concentration (m_s) is reduced or if the charge (z) is increased in either direction from the true isoelectric point. For a limited range of conditions, equation 3.7 or 3.9 predicts quantitatively the observed osmotic pressure-concentration curves.

For example, when albumin is equilibrated against .15 M NaCl ($m_s = .15$) at pH 7.4 the charge, z , is -17 , whence

$$\Pi = RT\left(c + \frac{17^2}{4 \times .15} c^2\right) \quad (3.10)$$

Taking 69,000 as the molecular weight of albumin and expressing c in g per 100 ml this becomes

$$\Pi = 2.8c + 0.19c^2 \quad (3.11)$$

Equation 3.11 is almost identical with the first two

² Net charge, z , is defined as the algebraic sum of all charges on the ionizable constituents of the protein molecule plus those charges which result from binding of ions by the protein. In the case of serum albumin at pH 7.4 in .15 M NaCl at 25°C the net charge estimated from the titration curve is -17 , made up of approximately 100 negative and 83 positive charges on the protein. In addition 9 or 10 chloride ions are bound to each molecule (86).

terms of the empirical equation 3.4 describing the observed osmotic pressure-concentration curve for albumin under the stated conditions (fig. 3.1). This close correspondence between observed osmotic pressure and the pressure calculated on the basis of Donnan theory might lead one to believe that the problem has been solved. Unfortunately, this is not the case. The correspondence between theory and fact only occurs at two particular values of charge, one of which occurs (fortuitously) at physiological pH and salt concentration. Figure 3.5 shows clearly the discrepancy between observed osmotic pressure and the theoretical pressure predicted on the basis of Donnan theory and van't Hoff's law. This discrepancy may be explained in part by the binding of chloride ions to the albumin molecule (86, 315). Binding of chloride (or other anions) to the protein decreases the fraction of salt free to take part in the Donnan distribution and at the same time causes an error in the calculation of net charge from titration data. For this reason, also, the isoelectric point differs from the isoionic point (86). When corrections are made for chloride binding it appears that the true isoelectric point for albumin is closer to pH 4.2 than to pH 5.4 as might be inferred from its titration curve. As shown in figure 3.5, the osmotic pressure does approach the van't Hoff pressure at pH 4.2 as would be

predicted from the Donnan relation (equation 3.6) for the case $z = 0$.

Even after corrections have been made for chloride binding, however, the Donnan theory fails to account quantitatively for observed osmotic pressure under most circumstances. Other factors involved include electrostatic interactions between protein molecules and between protein and salt. These interactions are presumably represented in the third term of the empirical equations (e.g., equation 3.4) describing osmotic pressure-concentration curves, but no precise theoretical explanation of these forces can be offered at the present time.

4. INTERSTITIAL FLUID PRESSURE ("TISSUE PRESSURE"), P_{if}

Capillary blood pressure is only one point on the transmural gradient of hydrostatic pressure which is concerned with the filtration of fluid through the capillary wall. The other point is the pressure on the interstitial fluid outside the capillary wall. Landerer (197) in 1884 attempted the first direct measurements of interstitial fluid pressure by introducing a fine cannula or needle into the subcutaneous or cutaneous tissues and recording the pressures required to cause fluid to flow into the tissues. Landerer's figures, like those of Hajen (139) and others (158, 252) proved to be fallacious because too much fluid was injected before pressure was measured (238). Nevertheless these experiments were significant because they showed that considerable resistance must be overcome if the volume of interstitial fluid is increased suddenly.

Even when the volume of interstitial fluid was increased more gradually and physiologically, evidence of mounting interstitial fluid pressure appeared almost at once, at least in some tissues. Drury & Jones (80) used an ordinary plethysmograph to measure rates of filtration in the leg during venous congestion, and found this rate declined as filtration progressed, though their figures were irregular because their method measured changes of vascular volume and of interstitial fluid volume together. A "pressure plethysmograph" (188, 209) made it possible to exclude changes of vascular volume and thereby to measure changes of interstitial fluid volume more accurately. Landis & Gibbon (209) found in the human forearm that the filtration produced by given venous pressures declined rapidly, beginning even during the first 10 min of filtration. With a venous pressure of 20 cm of water, filtration ceased in 35 to 55 min after the accumulation of less than 1 ml of filtrate per 100 ml

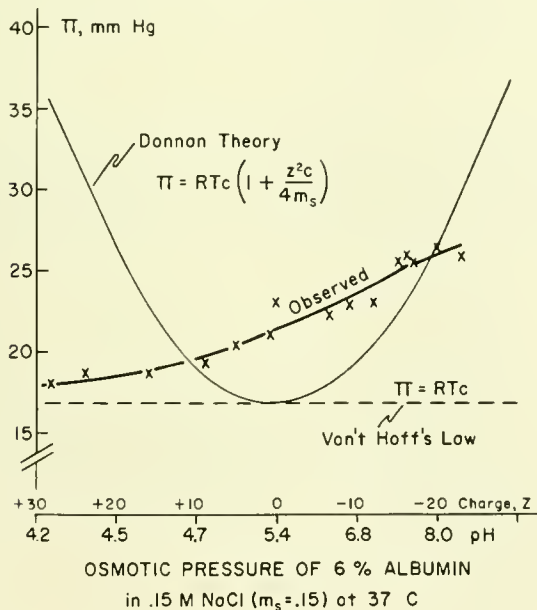


FIG. 3.5. Illustrating the discrepancy between osmotic pressure calculated on the basis of Donnan theory and protein osmotic pressure measured experimentally. Agreement with theory occurs fortuitously at pH 4.7 and pH 7.6. [Calculated from data in reference (313).]

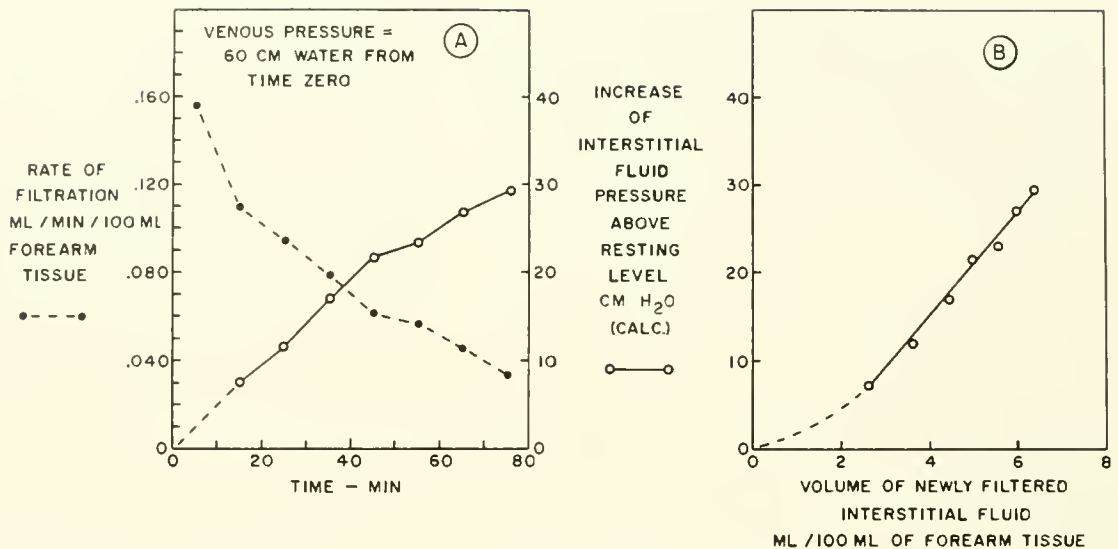


FIG. 4.1. Chart showing decreasing filtration rate (----- in *A*) measured in human forearm by pressure plethysmograph when venous pressure was elevated to 60 cm H₂O for 80 min. Interstitial fluid pressure (O—O) was calculated by dividing the cumulative decrease of observed filtration rates by the previously determined average normal filtration coefficient (.0033 ml/100 ml forearm tissue/min/cm H₂O increase of venous pressure), and then correcting each value for the local increase of plasma protein concentration and of Π_{pl} produced by net filtration. As shown in *A* calculated interstitial fluid pressure increases steadily with time, reaching a maximum of almost 30 cm H₂O by 75 min. In *B* the same calculated interstitial fluid pressures are charted against the cumulative volume of added interstitial fluid. As the interstitial compartment is distended by an increasing volume of filtered fluid, interstitial pressure in the forearm tissues probably rises slowly at first and then more rapidly. [Recalculated from data of Landis & Gibbon (209).]

of forearm tissue. As shown in figure 4.1 (*left*) when venous pressure was raised to 60 cm water, the initial filtration rate was .156 ml per min per 100 ml of forearm tissue but declined rapidly to less than .040 after 75 min of congestion. At this time the volume of newly filtered fluid was approximately 6 ml per 100 ml of tissue, i.e., about 60 per cent of the amount which produces manifest edema, detectable by "pitting on pressure." Knowing the decrease of filtration rate, the normal filtration coefficient (209), and, approximately, the increase in the osmotic pressure of the plasma proteins of the blood in the congested forearm (188, 211), it is possible to calculate interstitial fluid pressure, with results shown in figure 4.1.

Accumulations of interstitial fluid from prior filtration also increased the rate at which extravascular fluid was removed from the forearm (188, 209), as would be expected with higher interstitial fluid pressures. It is still impossible to decide to what extent this fluid was removed via the blood capillaries by absorption or via lymphatics by flow, though indirect evidence (188) indicated that small accumulations were probably removed by the former, larger accumulations by the latter in addition. The importance of

interstitial fluid pressure seemed clear, although dependable direct measurements were not available as yet.

In a review of this topic in 1934 (207) it was necessary to consider the conflicting views then current concerning bound and free water in the interstitial fluid compartment. It is now generally agreed on the basis of many studies by several dilution methods that the volume of truly "bound water" is negligible. Yet in normal tissues interstitial fluid cannot be identified microscopically as a distinct and continuous compartment or layer around capillaries or between cells except in a few locations. This is not surprising because a simple calculation shows that if the normal volume of interstitial fluid, approximately 15 per cent of gross tissue volume, is distributed uniformly between surfaces of cells, connective tissue fibrils, blood capillaries, etc., the average thickness of this layer cannot be greater than 1 μ and is probably less than 0.5 μ . This coincides with the findings of McMaster & Parsons (240, 241) who injected dye solutions into small lymphatic vessels and observed under high magnification that the dye penetrated into the tissues in the form of hair-like projections or "bristles,"

apparently between or along connective tissue fibrils (fig. 4.2). Hemorrhage and dehydration, which they used to diminish the volume of interstitial fluid, delayed the appearance of these bristles of dye, but eventually they became clearer than usual, as well as more resistant to displacement by massage. On the other hand, hydremic plethora, and particularly the edema of inflammation, tended to obliterate the bristles and permitted instead a diffuse and more rapid distribution of dye which could easily be displaced by pressure from one area into another, presumably because it dissolved in a larger and more freely movable volume of edema fluid.

The paucity of normal interstitial fluid, its layered distribution, and the disruptive effects of injecting even small volumes of fluid (238) makes it necessary, as with capillary blood pressure, to determine interstitial fluid pressure by a "null point" method which provides a balance of pressures with minimal movement of fluid into, or out of, the interstitial fluid compartment. Wells *et al.* (375) used a capillary tube placed between the manometer and the saline-filled needle that was inserted into the tissue. By observing the meniscus under a microscope, they saw that a

change of 2 or 3 mm water pressure sufficed to reverse the flow at the point of balance and hence, after correcting for capillarity in the tube, they measured interstitial fluid pressure with a small volume artifact. Burch & Sodeman (30) and McMaster (238) reduced the volume change further, but still more refined methods are needed to reduce the likelihood of local hemorrhage and mechanical artifacts.

Table 4.1 summarizes several representative series of values given in mm Hg for easier comparison with capillary blood pressure and the osmotic pressure of the plasma proteins. In skin, McMaster (238) found it necessary to determine "interstitial resistance" to very slow rates of inflow of fluid because paucity of freely movable fluid prevented determining a true interstitial pressure. Although some of the values in table 4.1 may be artificially high, their order of magnitude is consistent. P_{if} in skin and subcutaneous tissues, under resting conditions, ranges from 1 to 5 or 6 mm Hg and averages about 2.5 mm Hg. In muscle, P_{if} tends to be slightly higher, 1 to 9 mm Hg and averages 4.5 mm Hg. In some comparisons P_{if} was higher in the tightly sheathed muscles, e.g., soleus and anterior tibial, than in the more loosely enclosed

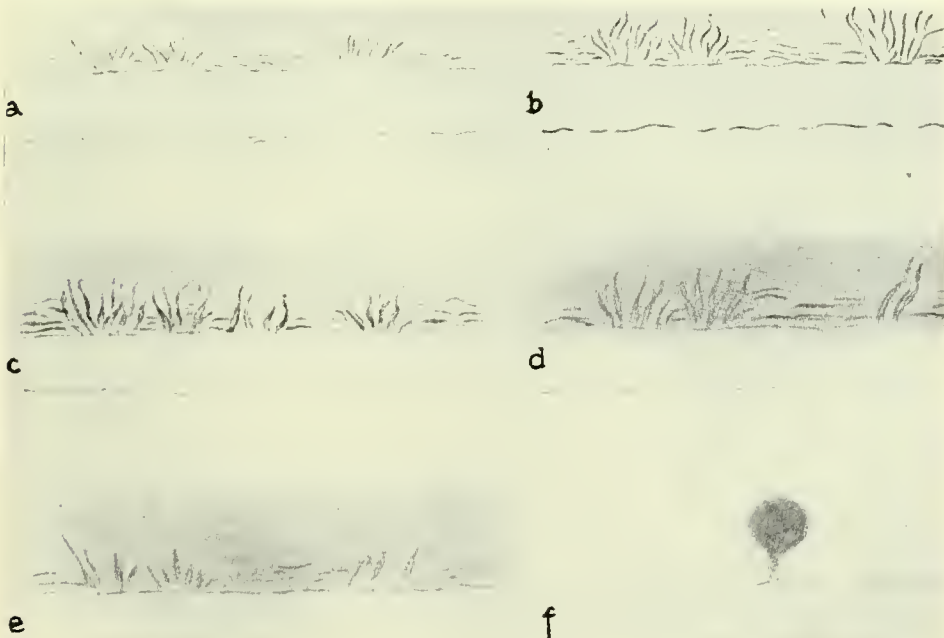


FIG. 4.2. Diagrammatic sketch of the extravascular interstitial movement of a 2% solution of pontamine sky blue after its escape from the lymphatics. *a*: Dye first appears as colored bristles at 2-7 min. *b*: Color becomes more intense and bristles longer at 3-10 min. *c*: Colored lines become broader at 5-12 min. *d*: Second phase. Diffuse blue staining between bristles which cannot be dislodged by pressure. Bristles disappearing. During *a* to *d* color was apparently fixed on tissue elements and not dislodged by pressure. *e*: Diffuse blue cloud easily displaced with pressure, free fluid. *f*: Dye escaping from ruptured lymphatics, no bristles. [From McMaster & Parsons (240).]

TABLE 4 1. *Interstitial Fluid Pressure, P_{if} , Ranges at Rest*

| Tissue, Species | Pressure (Range) mm Hg | Reference |
|-------------------|---------------------------|-----------|
| Subcutaneous, man | | |
| Forearm and leg | 1.5-5.1 | (375) |
| Foot | 1.1-3.2 | (30) |
| Pretibial | 1.3-4.0 | (30) |
| Forearm | 0.8-2.9 | (30) |
| Hand | 0.6-2.2 | (30) |
| Foot | 1.2-3.0 | (231) |
| Leg | 4.1-6.5 | (231) |
| Eyelid | 1.2-3.0 | (28) |
| Cutaneous | | |
| Mouse* | 0.4-3.7 | (238) |
| Man* | 1.8-4.9 | (238) |
| Muscle, man | | |
| Gastrocnemius | 0.7-3.7 | (375) |
| Soleus | 3.7-7.3 | (375) |
| Gastrocnemius | 2.6-8.9 | (231) |
| Biceps | 3.2-6.6 | (231) |
| Biceps | 2.9-6.6 | (127-129) |

* "Interstitial resistance" to very slow flow, probably 0.5 mm above P_{if} (238).

gastrocnemius and biceps (375). Very high pressures, up to 85 mm Hg, were found briefly in some muscles during powerful contractions (375), and values lower than average were common during anesthesia, hemorrhage, surgical operations, and shock (127-129).

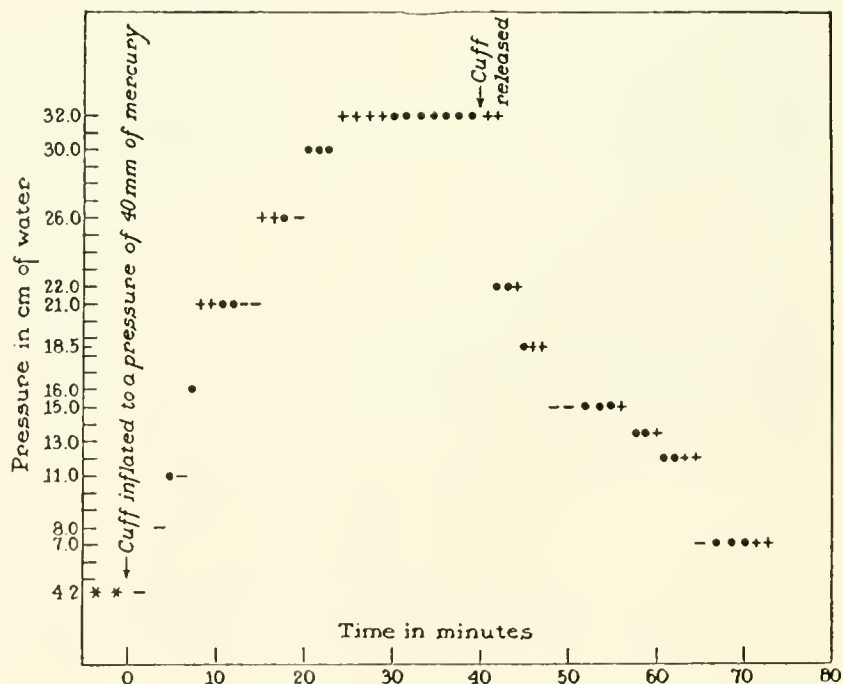
The effects of venous congestion, and consequent filtration, on directly measured P_{if} have been highly variable, depending, as might be expected, upon the

distensibility of the tissue studied. McMaster (239) found pressures up to 32 cm water or 23 mm Hg in the skin of the mouse (fig. 4.3), and up to 23 cm water or 17 mm Hg in human skin, in good agreement with the calculated interstitial fluid pressures found by Landis & Gibbon (209) in the congested forearm (fig. 4.1). Mayerson & Burch (231) found much lower maximum pressures in subcutaneous tissue of man during venous congestion or during quiet standing, e.g., 5.6 to 8.8 cm water, while intramuscular pressure rose to maxima of 22 cm water in nonfainting subjects and only 11 cm water in fainting subjects.

In isolated, perfused extremities Hyman (162) and Pappenheimer & Soto-Rivera (282) found little interference with prolonged filtration, and hence no evidence of increased interstitial fluid pressure, until manifest edema appeared. Hinshaw & Day (155), however, made direct measurements of P_{if} in perfused extremities and found increases from control values of 0.5 and 1.2 mm Hg to 8 and 15 mm Hg when 1+ edema was present and to 10.5 and 24 mm Hg when 2+ edema had appeared. This pressure was enough to produce measurable collapse of blood vessels. If this collapse involves the small veins it may well distort fluid movement through changes in resistance to flow, as well as through direct opposition to capillary blood pressure itself.

Interstitial fluid pressures up to 25 mm Hg help explain the slowness with which edema forms in normal human beings, despite the high capillary pres-

FIG. 4.3. Changes of interstitial fluid pressure in the skin and lower leg of mouse during and after venous congestion of 40 mm Hg. Black dots indicate pressure readings which yielded neither inflow into the skin nor backflow into the apparatus; i.e., the pressure of the extravascular fluid was accurately balanced. Plus signs indicate pressure readings at which fluid moved into the tissues; i.e., pressure in the apparatus was above interstitial pressure. Minus signs show that backflow occurred into the apparatus and that the plotted pressure was lower than that of the extravascular fluid. The interstitial resistance during the control period is shown by asterisks. [From McMaster (239).]



tures and rapid initial filtration found in the lower extremities during sitting or quiet standing. However, the occurrence of edema indicates, of itself, that the tissue elements are slowly separable, and so cannot resist higher than normal interstitial fluid pressures indefinitely. P_{if} in manifest edema of man has proved to be highly variable though frequently above normal limits. During accumulation of edema fluid it ranged from 4 to 18 cm water in one series (336) and from 4 to 26 cm water in others (30, 340), returning in all instances toward normal or below as the edema fluid disappeared. Holland & Meyer (158) reported pressures below normal in edema, but their method was open to question (238). In the skin of the mouse McMaster (238) found that P_{if} was little elevated in some forms of experimental edema and greatly elevated in others with the further anomaly that in some instances beefy indurations occurred in which paucity of freely movable fluid permitted only measurement of interstitial resistance to slow introduction of fluid. In general, both clinically and experimentally, the highest interstitial fluid pressures were found in skin which had become recently and rapidly edematous. Slowly developing edema often occurred without significant elevations of P_{if} . The distensibility of tissues is also an important variable. The eyelids accommodated rapidly injected fluid most easily, the face and pretibial areas least easily (28). In edema P_{if} was found to be lower, 1 to 8 cm water in the former and higher, 2 to 14 cm water, in the latter.

The limited and transitory resistance of tissues to slowly introduced fluid has been described quantitatively by McMaster (237). At pressures ranging from 4.5 to 14 cm water the entry of Locke-Ringer's solution through a needle into a tissue was slow and also intermittent. Above these pressures, which he termed the "breaking point," fluid flowed into the tissue continuously and at much higher rates, which increased linearly with further pressure increments. Once the tissues had been separated by this "breaking pressure," high rates of flow were observed even at low pressures (237). The resistance which the normal interstitium offers to flow of filtered fluid from capillaries to lymphatics has been demonstrated in different fashion recently during venous congestion in the dog's leg by Irisawa & Rushmer (166). When venous pressure was elevated to between 65 and 55 cm water for 270 min the pressure in the draining lymphatic vessels rose very slowly reaching, after 90 min, plateaus of 18 cm water or less.

The positive interstitial fluid pressures so far described were obtained in acute experiments of rela-

tively brief duration. There is some evidence, however, that interstitial fluid pressure may be slightly but definitely negative under some conditions and in more prolonged observations. McMaster (235, 236) observed at atmospheric pressures that fluid flowed intermittently from a needle into cutaneous tissue at rates up to .08 mm³ per min. This suggests a negative interstitial pressure, but the subatmospheric pressure required to arrest inflow was not determined. Inflow of fluid was increased in transitory fashion by painful stimuli and by the intravenous injection of hypertonic sucrose solution. These changes are explicable on the basis of increased absorption by capillaries during vasoconstriction and decreased capillary blood pressure in the first instance, and by temporary hypertonicity of capillary blood in the second instance. Outflow of fluid, that could be arrested by positive pressure on the fluid in the needle, was found during venous congestion and when an irritant solution produced localized edema. These outflows may be explained respectively by heightened capillary pressure and by injury. On the other hand, the hyperemia induced by heat, either directly or reflexly, increased inflow of fluid into the tissue, despite observed vasodilatation and presumable elevation of capillary pressure. It is possible that locally increased arterial pulsation may, by pumping action, have evacuated the regional lymphatics and so increased inflow mechanically (283, 373).

Very recently Guyton *et al.* (130) have extended the time of observation to hours or days. Immediately after insertion of needles, and in agreement with previous studies, slightly positive readings, e.g., +1 to +2 cm water, were obtained. During the next 4 or 5 hours, however, the balancing, null-point pressures decreased gradually to -2 or -3 cm water with indications that this decline was still continuing. To extend readings to days or weeks, perforated plastic capsules were implanted in the subcutaneous tissue and after 1 or 2 weeks pressures were -3 to -14 cm water in the abdominal wall, axillary space, scrotum, muscle, and quiet limb. They decreased slowly, over a period of minutes, when the respective parts of the body were moved. Venous congestion changed the pressure to positive values, but not until edema was apparent. Protein in the capsule also produced positive values.

Chronic experiments of this type tend to avoid some of the artifacts, e.g., acute reactions to the insertion of a needle or pipette, that may influence immediate measurements of interstitial fluid pressures. On the other hand, their long duration introduces the possibility of slower reactions to foreign bodies, including

local changes of pressure from contraction of fibrin strands or of newly formed connective tissue. It may be, too, as Guyton suggests, that the negative pressures result in part from intermittent evacuation of lymphatics by the mechanical pumping which accompanies movement.

Again, the kidney has proved to be a special case. Gottschalk (123) found interstitial fluid pressures averaging +10 mm Hg in rats, guinea pigs, rabbits, and cats, and +16 mm Hg in dogs. These pressures rose promptly whenever renal venous pressure or ureteral pressure was increased. Inside the renal capsule the pressures in tubules, peritubular capillaries, and the interstitium changed together, and by approximately equal increments, without evidence of the breaking pressure found by McMaster (237) in skin and subcutaneous tissue. It seems clear that interstitial fluid pressure, like capillary blood pressure, must be considered tissue by tissue.

5. PROTEINS IN EXTRACAPILLARY FLUIDS; Π_{if}

A. Capillary Filtrate From Limb Capillaries; Protein Content

The concentration of protein in the fluid which is filtered through the capillary wall is an important figure for several reasons. In the first place, it is the most direct measure of capillary permeability to protein, and hence of the effectiveness of the capillary wall as a protein-retaining membrane. Second, this original capillary filtrate is the raw material from which interstitial fluid, and eventually lymph, are produced. Third, just as filtration is produced by $P_c - P_{if}$, so absorption is produced by $\Pi_{pl} - \Pi_{if}$, i.e., by the effective osmotic pressure of the plasma proteins. Fourth, studies on the volumes and protein concentrations of capillary filtrates in various tissues, and under various conditions, have established the existence and approximate magnitude of a physiologically important circulation of protein from capillary blood, through the interstitial fluid compartment around the tissue cells, thence to the lymphatics, lymph nodes and via the lymphatic trunks back to the circulatory system.

By 1898 large regional differences in the concentration of protein in lymph were well known, and corresponding differences in the permeability of capillary walls to protein were postulated. Thus Starling wrote: "The lymph in the limbs, the filtrate through the impermeable limb capillaries, contains only from 2 to 3 per cent proteids; that from the intestines contains

from 4 to 6 per cent proteids; while that from the permeable capillaries of the liver contains from 6 to 8 per cent proteids—in fact almost as much as the blood plasma itself" (346). Over half a century of work on lymph has confirmed these figures, providing some allowance is made for improved analytic methods. In the most recent compilations (79, 386) the total protein in lymph from legs at rest ranged from 1.3 to 3.3 g per 100 ml; from intestine, 2.8 to 4.0, and from liver, 4.4 to 6.1. However, the interpretation of these figures, particularly with respect to the lymph from the limbs, has changed. Starling (346) and also Drinker & Yoffey (79) believed that the protein content of lymph and of interstitial fluid must be identical, a view that now is not tenable. Hence it is helpful to consider in sequence *a*) the protein content of the original capillary filtrate, *b*) the fate of this protein as the capillaries absorb fluid, *c*) the resulting protein content of interstitial fluid, and, finally, *d*) the protein content of lymph. For reasons already described in the previous section it has so far proved impossible to collect normal capillary filtrate directly. However, for limb capillaries relatively consistent estimates of the protein content of capillary filtrate have been obtained indirectly *a*) from analyses of certain edema fluids, *b*) from studies of plasma proteins during venous congestion, and *c*) from studies of lymph during venous congestion and during chronic plasmapheresis.

In severe hypoproteinemic edemas, e.g., nephrosis, malnutrition, and amyloid disease, absorption is presumably abolished because of the lowered osmotic pressure of the plasma proteins. Hence, as previously reviewed (207), the presence in these edema fluids of 0.09 to 0.40 per cent of protein, with most values between 0.1 and 0.27 per cent, provided the first estimates of the protein content of capillary filtrate with the reservation, however, that disease may have modified the permeability of the capillary walls. In cardiac failure, edema fluids contained from 0.1 to 1.0 per cent protein with an average of 0.4 per cent.

In normal subjects, elevating venous pressure to 25 mm Hg or more, i.e., to exceed the osmotic pressure of the plasma proteins, also abolishes absorption of fluid. Landis *et al.* (211) congested the forearms of human subjects and computed from the hematocrit ratios of venous blood the volume of filtrate from each 100 ml blood plasma, and divided this into the amount of protein simultaneously lost from the plasma during the same congestion. The errors involved in small filtered volumes, and even in triplicate protein analyses, prevented any conclusions with congestions of 40 mm Hg; but at 60 mm Hg the calcu-

lated average protein content of the filtrate was about 0.3 g per 100 ml of filtrate, though with very wide variations. At a venous pressure of 80 mm Hg the average protein content of capillary filtrate was 1.5 g per 100 ml, but this was attributed to leakage because of marked vascular distention and slowed blood flow with possible increased permeability from local hypoxia. Fractionation studies of plasma proteins before and after congestion indicated qualitatively that capillary filtrate contained both albumin and globulin. All that this approach could provide, however, was a rough order of magnitude for the normal protein content of capillary filtrate. It indicated merely that it was, on the average, considerably less than the protein content of lymph. In passing, it should be emphasized that this venous congestion method is of doubtful utility in measuring capillary permeability to protein in individual patients with various diseases (e.g., 6, 32, 33) because normal values vary greatly from subject to subject even under carefully controlled conditions (17, 211). The reasons for this variability are still not clear. Probable factors are streamline flow in veins with sampling errors and, in addition, analytic errors even with triplicate hematocrits and protein analyses.

Shortly after the studies of Landis *et al.* (211), White *et al.* (379) approached the problem more directly and found that venous congestion of the dog's leg reduced the concentration of protein in lymph from 0.77 per cent to 0.21 per cent while the rate of lymph production increased sixfold, as would be expected with exclusion of absorption. In another experiment lymph protein fell during venous congestion from 1.24 per cent to 0.78, but lymph flow failed to increase as much as in the previous experiment, and the lymph contained a considerable number of erythrocytes. By still another method Pappenheimer & Soto-Rivera (282) found in the perfused hind limbs of cats that capillary filtrate contained an average of 0.3 per cent protein with values of 0.2 and 0.4 per cent falling within the range of error.

Thus, in mechanical, i.e., noninflammatory, edemas and in congestion of the human forearm, the capillary walls were found to be approximately 95 per cent effective as protein-retaining membranes (207). During rapid filtration the protein concentration of capillary filtrates is extremely small even in the more permeable capillaries of the intestine (168a). It is probable that under these conditions the protein concentration is reduced by molecular sieving as discussed in sections 7D and 10.

Concerning the fate of the protein that has passed from the blood stream with capillary filtrate into the

interstitial fluid compartment, information is far from complete though generally in favor of minimal re-entry into capillary blood despite absorption of fluid. Lewis (215) injected horse serum subcutaneously in dogs and detected it in thoracic duct lymph within 40 min., but in blood only after 3.5 hours. Field & Drinker (97) also injected horse serum subcutaneously into dogs and found, by a precipitin reaction, that when all possible lymphatics were blocked no foreign serum could be detected in the blood stream in periods up to 7 hours after injection. They concluded that the blood capillaries of the subcutaneous tissues are not ordinarily concerned in the absorption of protein. Courtice *et al.* (56, 58, 59) injected plasma protein labeled with T-1824, into the peritoneal cavity and recovered nearly all of it in lymph. Jepson *et al.* (167) followed the removal from skin of protein labeled with I^{131} and in normal dogs found that lymph exhibited far more radioactivity than blood plasma. From similar studies in man, Hollander *et al.* (159) concluded that protein is returned to the circulation chiefly or exclusively by lymphatic flow. In the lung of dogs, however, Drinker *et al.* (78) found that protein injected into the alveoli appeared first in blood though very slowly and in small amount.

It seems likely that most of the protein in capillary filtrate normally fails to enter capillary blood, even during absorption of fluid, because such direct return to plasma involves the movement of protein molecules against a considerable concentration gradient. More information is needed because the mechanism and completeness of this exclusion of protein during absorption of fluid is still far from clear, particularly in abnormal states. Thus, Field & Drinker (98) found in dogs with ligated lymphatics that acute plasmapheresis increased the absorption of foreign protein from the tissue spaces. Jepson *et al.* (167) found this true of labeled protein in lymphedema also.

B. Interstitial Fluid; Protein Content and Π_{if}

The protein content of interstitial fluid under normal, resting conditions, and the protein osmotic pressure of that fluid, Π_{if} , have also been determined so far only by indirect methods. The protein concentration in capillary filtrate being 0.2 to 0.4 g per 100 ml, and that in lymph from a resting extremity being 1.3 to 3.3 g per 100 ml it follows that the protein content of interstitial fluid under resting conditions lies between these figures and is not uniform. Depending upon localized filtration or absorption, it can range from protein-poor capillary filtrate, just produced, to an interstitial fluid which is protein rich

at the end of absorption and about to enter the lymphatic system. Pappenheimer & Soto-Rivera (282) have pointed out that the diffusion coefficients of the plasma proteins are such that in the absence of flow or mechanical movement relatively large concentration gradients are possible in the interstitial fluid compartment. "Even if all filtration and absorption processes were stopped, some 20 minutes would be required to reach 90 per cent equalization of protein concentration over a distance of 50 microns" (282). In perfused limbs of cats the average protein osmotic pressure of interstitial fluid was 1.4 ± 0.4 mm Hg, corresponding to an average protein concentration of 0.7 ± 0.2 g per 100 ml.

The average concentration of proteins in interstitial fluid can also be estimated by a totally different method. The dilution of labeled plasma albumins and globulins after intravenous injection has shown that the total mass of exchangeable plasma protein is about twice the mass of plasma proteins in the blood stream itself (103, 117). Sterling (352) found in man that the average intravascular albumin averaged 117 g, the extracellular albumin, 147 g. Assuming extravascular fluid volume to be the usual 15 per cent of body weight, the average albumin concentration in extravascular fluid was calculated to be 1.4 g per 100 ml. By using Myant's figures (259) to estimate globulin content in addition, the total average protein concentration for extravascular fluid becomes approximately 2.1 g per 100 ml, which corresponds to an average protein osmotic pressure, or Π_{if} , of 5 mm Hg. Similar calculations applied to the data of Wasserman *et al.* (368, 372) yield slightly lower figures, because in the dog the fraction of albumin and globulin found normally in the interstitial fluid and lymph appears to be rather less than that found by Sterling for albumin in man. Both estimates are larger than those given by Pappenheimer and Soto-Rivera (282) for the perfused leg of dogs as expected, because the determinations made by the perfusion method were restricted to the fluid in the immediate vicinity of the capillaries and were limited to the limb, both factors tending to give lower values. On the other hand, calculations based upon exchangeable protein mass include protein in the whole of the interstitial fluid plus that in the lymphatics. In addition, they include the extravascular fluids of the liver and intestines where lymph is known to contain large amounts of protein. Both factors tend to make the figure for average Π_{if} greater for the whole body than for the limb alone, but still not as high as that probably present in the liver and intestines.

With this qualification it can be concluded that Π_{if} lies between 0.1 and 5.0 mm Hg, with the lower value applying to capillary filtrate in the limbs and the higher including the total interstitial fluid of liver and intestines, as well as lymph. This can be compared to P_{if} which ranges from 1 to 9 mm Hg, with the lower values in subcutaneous tissues and skin, the higher values in muscle. The formulation given in equation 1.1 can now, with certain license for purposes of summary, be provided with very approximate values in mm Hg for man at heart level and under resting conditions, viz.:

$$F.M. = k(P_c - \Pi_{pl} - P_{if} + \Pi_{if})$$

| | | | | |
|-------------------------|----|----|--------|----------|
| $+ = \text{filtration}$ | 32 | 25 | 1 to 9 | 0.1 to 5 |
| $- = \text{absorption}$ | 15 | | | |

With equal or greater license an average limb capillary and lymphatic can be drawn, as in figure 5.1, to summarize the filtration-absorption process as it may operate to produce a small volume of lymph with relatively high protein content. Table 5.1 provides a schematic summary of the changes that occur in the fluids of the limb during several of the more thoroughly studied functional states. Ranges of determined values are given whenever possible. Figures in parentheses are values that can reasonably be inferred on the basis of available evidence. They are given merely to show the probable direction of presumed change and its order of magnitude. In some instances even inferences are impossible, as indicated by a question mark. The columns are given letters to correspond with the schematic capillary in figure 5.1.

Beginning at the top of the table with control conditions and resting blood flow, the composition of capillary filtrate has not been determined, but its protein content may be inferred to be 0.2 to 0.4 g per 100 ml from the composition of capillary filtrate produced during mild venous congestion in man and dog. The average protein content of interstitial fluid ranges from 0.7 g per 100 ml in perfusion studies (281) to 2.1 g per 100 ml by calculation from extravascular protein mass. Lymph protein content range from 1.3 to 3.3 g per 100 ml (386) and the volume flow is small, requiring massage or passive movement for collection of samples (76) as would be expected with the absorption that occurs under resting conditions.

Conversely, in venous congestion the protein concentration in capillary filtrate is known but the average and highest concentrations in interstitial

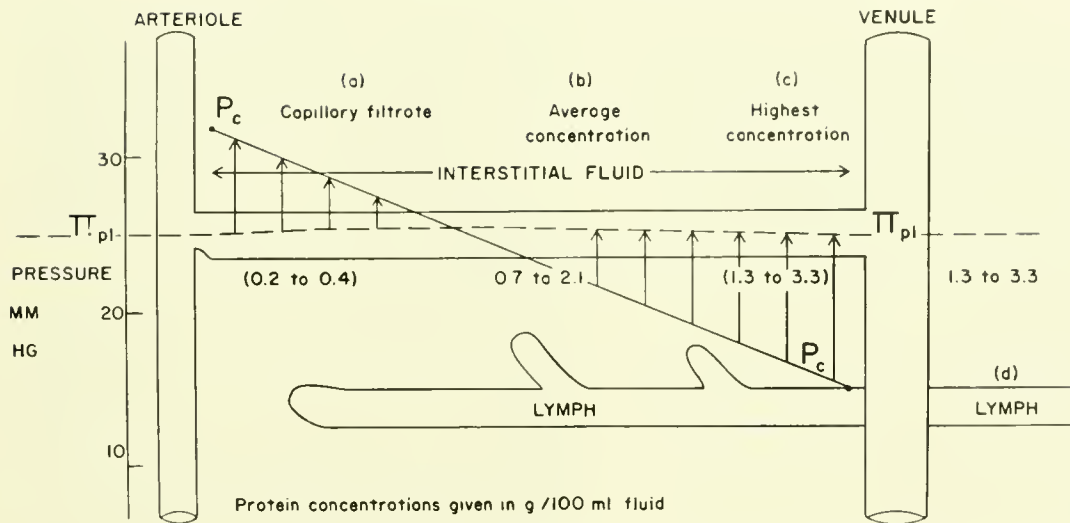


FIG. 5.1. Schematic diagram of "an average limb capillary" to indicate approximate protein concentrations in capillary filtrate, interstitial fluid, and lymph.

TABLE 5.1. Protein Concentrations in Extravascular Fluids of the Limb

| Condition | Capillary Filtrate a | Interstitial Fluid | | Lymph d |
|-------------------|-------------------------|--------------------|--------------------|------------|
| | | Avg conc. b | Highest conc. c | |
| | g/100 ml | g/100 ml | g/100 ml | g/100 ml |
| Normal, resting | (0.2-0.4) | 0.7-2.1 | (1.3-3.3) | 1.3-3.3 |
| Venous congestion | 0.2-0.4 | (0.2-0.4) | (0.2-0.8) | 0.2-0.8 |
| Hypoproteinemia | (0.01-0.4) | 0.04-0.5 | (0.01-0.6) | 0.01-0.6 |
| Burns | (3.5-5.0) | (3.5-5.0) | (3.5-5.0) | 3.5-5.0 |
| Muscular activity | ? | ? | (0.5-1.5) | 0.5-1.5 |
| Lymphedema | ? | 1.9-3.5 | ? | 2.3-3.4 |

fluid have to be inferred from studies on lymph. This inference is valid after newly formed capillary filtrate has washed out of the interstitial compartment the fluid which was present before congestion and while the interstitial fluid compartment is being constantly irrigated by newly formed capillary filtrate with no absorption possible.

Hypoproteinemia in man, as mentioned above, produces edema fluids with protein concentrations ranging from 0.09 to 0.40 per cent. Weech *et al.* (374) used chronic plasmapheresis to produce severe edema of this type in dogs. Edema fluid contained between 0.04 and 0.4 g protein per 100 ml with all but a few values below 0.25. Lymph protein in the same ani-

mals ranged from 0.01 to 0.6, with almost all values below 0.3. In some instances the protein content of edema fluid was slightly higher than that of lymph collected simultaneously, indicating again the possibility of imperfect mixing of the interstitial fluid compartment and, consequently, some sequestration of edema fluid. Capillary filtrate, however, has not been studied and so its protein content can only be inferred. Lessened permeability to protein has been suggested (374) but not proved so far. Sieving of protein molecules may be involved (see section 10).

Massive injury in burns, produced by immersing the extremities of anesthetized dogs in hot water (48, 99, 100, 119, 120) increases lymph flow conspicuously and increases the protein in lymph to between 3.5 and 5 g per 100 ml. In view of the known effects of injury on capillary permeability to protein (200) it is safe to infer that protein concentrations in capillary filtrate and interstitial fluid are equally high; particularly because lymph flow is rapid and the interstitial compartment is well irrigated by capillary filtrate.

For contracting muscle, information is still meager. White *et al.* (379) found in dogs that while the flow of lymph was much increased by exercise, its protein content declined to between 0.5 and 1.5 per cent, average 1.0, and then remained constant as long as exercise continued. The elevations of capillary blood pressure and of interstitial fluid pressure during exercise have already been described in sections 2D and 4. Inferences concerning capillary filtrate and interstitial fluid are unjustified because the lymph col-

lected during exercise (379) contains more erythrocytes than control lymph does. This finding suggests mechanical rupture of some capillaries, probably when compressed between adjacent contracting fibers. If this occurs, undetermined amounts of whole plasma may accompany the erythrocytes and contribute to the protein found in lymph. The possibility of osmotic shifts of fluid produced by small molecules, e.g., lactic acid, from contracting muscle has also been proposed (207).

Finally, in lymphedema, the effect of obliterating lymph flow by obstructive fibrosis of the larger lymphatic vessels (77) is an accumulation of extravascular fluid with abnormally high concentrations of protein in both the edema fluid as well as in the stagnant lymph. The protein content of capillary filtrate is unknown and may be quite variable because of the tendency in lymph stasis toward intermittent infection and consequent injury to capillaries in severely lymphedematous extremities (77). It is clear that more information is needed in all these conditions.

C. Circulation of Interstitial Fluid; Circulation of Protein

It has been customary in the past to say that capillaries "leak" protein as if this were a useless defect of the capillary wall. However, many lines of evidence indicate that passage of plasma proteins through the capillary wall is quite as important for cellular metabolism and for defense against infection as the retention of plasma protein is for normal fluid balance. Whipple & Madden (376) showed that the circulating plasma proteins within the blood vessels form a "medium of exchange" which is an important part of a larger nutritional pool. For example, dogs were maintained in full nitrogen equilibrium by intravenous administration of dog plasma only. Drinker (75) called attention to the benefits derived, during infection, from the passage of globulins, including antibodies, through the capillary wall into the interstitial fluid around the cells and thence to the lymphatics. Still more recently several reviews have described the binding of hormones (63, 304), fatty acids (109), and drugs (121) to plasma proteins. It is significant, too, that the greatest passage of protein through the capillary walls occurs in the liver, where metabolic requirements are greatest and most varied, and where albumin is synthesized.

Two paracapillary circulations (i.e., beside and beyond the capillaries) can be identified. The first is a

filtration-absorption circulation which includes the total capillary filtrate, the total interstitial fluid, and finally that part of the interstitial fluid which passes back into the capillary blood by the process of absorption. The second paracapillary circulation begins also with capillary filtrate but then reduces to the unabsorbed fraction of interstitial fluid and its contained protein, both of which, after bathing the tissue cells, enter the finest lymphatic capillaries and are conducted, via the major lymphatic trunks, back to venous blood (see Chapter 30). Enough information is available now to justify approximate calculations of the magnitudes of these two circulations. Because both depend upon the total volume of capillary filtrate this figure can be considered first.

Continued blood flow through the resistance of the capillaries requires, even at resting flow rates, a significant pressure gradient in the capillary bed itself. As indicated in table 2.1 and figure 2.3 this average gradient lies above the osmotic pressure of the plasma proteins in the first half of the capillary network. It follows that, secondary to the basal pressure head which is necessary for this resting blood flow, there is necessarily a "basal filtration" of fluid under resting conditions. Most of this filtrate is absorbed and the low rates of lymph production in resting extremities can give no indication of the rate at which the original capillary filtrate is formed. A simple calculation suggests, however, that in the resting animal capillary filtrate is continuously produced at an average rate which is at least five to ten times greater than average resting lymph flow.

Landis & Gibbon (209) found in the human forearm at 34 to 35 C that elevating venous pressure by 1 cm H₂O increased filtrate by .0033 ml per 100 ml forearm tissue per min. Assuming that 80 per cent of a rise in venous pressure is transmitted to the capillaries, this becomes .0040 ml per 100 ml forearm tissue per min for a 1 cm water increase of capillary pressure. From capillary pressure measurements in human skin, mean resting filtering pressure is $(32 - 25 \text{ mm Hg})/2$ or 3.5 mm Hg, or 4.8 cm H₂O. Assuming, for the purpose of obtaining a minimum figure, that the unit increment of filtration given above applies to the whole body, the total resting capillary filtrate for a 75-kg human being is approximately 20 liters per 24 hours. To the extent that filtration coefficients in liver and intestine may be greater than in the forearm the volume of filtrate formed per 24 hours will be somewhat larger still.

For total lymph flow in man the most helpful data are those of Crandall *et al.* (60) obtained from a

patient with a freely draining fistula of the thoracic duct. Average basal lymph flow during fasting was 0.93 ml per min. After a heavy meal, flow from the thoracic duct reached a peak volume of 3.9 ml per min and remained above 1.0 ml per min for several hours. If allowance is made for the additional and uncollected lymph from the right lymphatic duct by adding an increment of one-fourth to one-third of fasting thoracic duct flow, then total lymph flow in fasting man at rest is approximately 2 liters per 24 hours. With allowance made for the effects of meals and activity, it probably approaches 3 or 4 liters per 24 hours.

Figure 5.2 shows schematically the volumes of these several "circulations" in terms of exchanges in 24 hours. With a cardiac output of 6.0 liters per min the first circulation, that of blood itself, amounts to about 8000 liters per 24 hours. From this volume, filtration in the capillary bed removes a minimum of 20 liters per 24 hours, a "filtration fraction" of 0.25 per cent. This capillary filtrate begins the second circulation, that of interstitial fluid (fig. 5.2, F to IF to A) with capillary absorption, during rest, of 80 to 90 per cent or 16 to 18 liters, of the original capillary

filtrate. The remaining 2 to 4 liters, including the unabsorbed protein of the original capillary filtrate, then produces the third circulation, that of proteins in lymph.

The potential magnitude of this protein circulation can be estimated from the observations of Wasserman & Mayerson (370-372) on the rates at which intravenously injected labeled albumin and globulin disappeared from plasma and appeared in thoracic duct lymph. The faster component of these two-phase disappearance curves indicated a steady disappearance of plasma albumin from plasma, and corresponding appearance in lymph, at the rate of approximately 0.1 per cent of the total circulating plasma protein per minute. Allowing for the slightly slower disappearance rate of globulin (372), this amounts to the passage through the capillary wall in 24 hours of a mass of plasma protein approximately equal to that in the circulating blood itself. This includes passage from the more permeable hepatic and intestinal capillaries as well as from the less permeable limb capillaries. Courtois (49; 386, p. 87) collected lymph simultaneously from the thoracic, right lymphatic, cervical, foreleg, and hind leg ducts. Expressed as percentage of total intravascular protein, the lymph collected from these several sources contained a 24-hour protein mass equaling, respectively, 47.5, 3.6, 2.4, 2.2, and 1.8 or, in total, 57.5 per cent of the intravascular protein mass. Again this rate of passage is a basal rate found in resting animals. Intravenous infusions increased the rate of protein passage severalfold (371) and increased lymph flow from the thoracic duct correspondingly (180), indicating that the interstitial circulation of both protein and fluid can be very rapid indeed. Studies during muscular exercise would be most interesting, but have not been done so far.

For man the magnitude of this protein circulation can be estimated in two ways. First, the obligatory capillary filtrate of 20 liters per 24 hours, containing 0.2 to 0.4 g per cent protein, would carry with it a minimum of 40 to 80 g of protein per 24 hours. This figure is unquestionably too low because it does not include the higher protein content of capillary filtrates from liver and intestine. Second, collections of thoracic duct lymph with analyses of protein content have been carried out in two patients with accidental fistulae (57, 60) and in patients with terminal neoplasm (15). As mentioned above, the data of Crandall *et al.* (60) justify an estimate of 2 to 4 liters of lymph per 24 hours. Since the protein content of this lymph ranged from 3.19 to 4.88 g per 100 ml the circulation

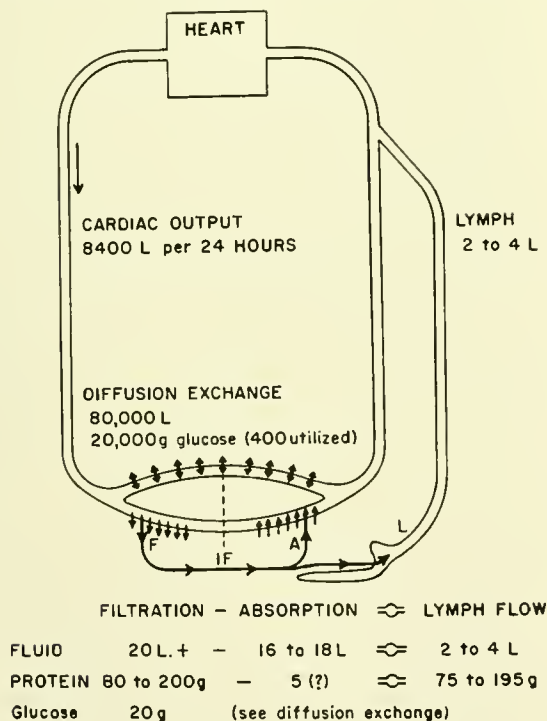


FIG. 5.2. Diagram of the "several circulations" with approximate magnitudes of each. For explanation of diffusion exchanges see section 9. For explanation of figures relating to filtration, absorption, and lymph flow see text of this section.

of protein can range from 60 to 200 g per 24 hours, depending upon conditions. Hence the third, or protein, circulation passing from capillaries to interstitial fluid to lymph (fig. 5.2, F-IF-L) involves daily a volume of fluid which approaches the volume of circulating plasma and a mass of protein equivalent to a quarter or more of the mass of the circulating plasma proteins. Cope & Litwin (45a) have recently emphasized the compensatory importance, during recovery from hemorrhage, of this continuing flow of lymph and its contained protein from the interstitial spaces into the blood stream.

6. FILTRATION COEFFICIENTS OF CAPILLARIES (k_c); AND OF TISSUES (k_t)

A. Normal Capillaries

Measurements of fluid movement through the capillary wall as a function of hydrostatic and osmotic pressures have been made in single capillaries of amphibian mesenteries (23, 200, 201, 383); in the human forearm (24, 188, 209); in the perfused extremities of frogs (61, 74); of rats (162, 302); of cats and dogs (281, 282); and in lung (132).

The primary measurements necessary to test the validity of the Starling hypothesis were first obtained by micromanipulation techniques in single capillaries of the frog's mesentery (200, 201) with results shown

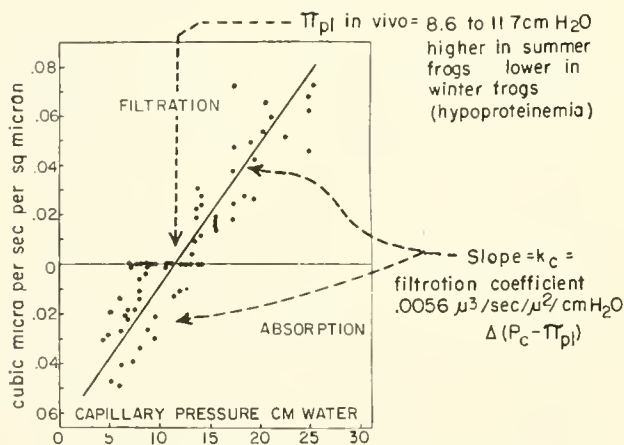


FIG. 6.1. Relation between fluid movement through walls of single capillaries of frog's mesentery and capillary blood pressure as determined by micromanipulation methods. Slope of line indicates filtration coefficient (k_c) in μ^3 of fluid filtered (or absorbed)/sec/ μ^2 of capillary wall/cm H_2O capillary pressure. Intercept of line with zero axis measures effective osmotic pressure (in vivo) of the plasma protein. [From Landis (200).]

in figure 6.1. When capillary pressure exceeded 12 cm water, fluid passed from the plasma inside the capillary to outside the capillary (filtration). When capillary pressure was less than 10 cm water, fluid was withdrawn from the extravascular space into the capillary (absorption). At capillary pressures between 9 and 13 cm water there were many instances in which little or no movement of fluid occurred. In this range hydrostatic pressure was apparently balanced by the osmotic pressure of the plasma proteins. This was taken to be indirect evidence that the walls of the mesenteric capillaries of the frog were relatively impermeable to protein and that, at least in these vessels, 9 to 13 cm water (average 11.5 cm) represented the effective osmotic pressure of the plasma proteins in vivo.

In addition to supporting the filtration-absorption hypothesis of Starling these results also provided the first measure of the permeability of the capillary wall to isotonic fluid. When plotted against capillary pressure the rates of fluid movement were directly proportional to the difference between the capillary pressure and the effective osmotic pressure of the plasma proteins measured against the capillary wall as a filter. The proportionality constant was computed from the slope of the straight line drawn through the observed points by the method of least squares. This was originally called a "filtration constant," but for reasons given below the term "filtration coefficient" is preferable (276). For normal mesenteric capillaries of the frog the filtration coefficient, k_c , derived from 70 observations, averaged $.0056 \mu^3$ of fluid per sec per μ^2 of capillary wall per cm water difference between capillary pressure and the osmotic pressure of the plasma proteins. Wind (383) found great variation from capillary to capillary in the toad's mesentery. Collectively, these figures provide a slightly lower average figure, about .0032, during the first 15 min after the mesentery was exposed and a somewhat higher average figure, .0084, thereafter. Deviations from these normal filtration coefficients have proved helpful, as will be described below, in measuring the effects of temperature (23), oxygen lack (201), and injury (200) on the filtration-absorption mechanism in the frog's mesenteric capillaries.

To test the validity of the Starling hypothesis in another tissue, and particularly in man, Krogh *et al.* (188) studied the movement of fluid through the capillary walls of forearm tissue in a pressure plethysmograph, by means of which the blood vessels could be collapsed in order to measure small increments of tissue volume produced by filtered fluid. As shown in

figure 6.2 net filtration of fluid increased linearly with venous pressures above 10 cm water. A unit rise of venous pressure (1 cm water) increased the filtration rate by .0023 ml per min per 100 ml of forearm tissue when congestion periods of 30 min were used (188) and by .0033 ml per min per 100 ml forearm tissue when congestion periods of 10 min were used (209). As described in section 4, this difference was regarded as the result of increasing interstitial fluid pressure as the volume of filtrate in the tissues increased.

Brown *et al.* (22) have more recently studied, by a totally different method, the filtration coefficient for the whole body of man (except the thorax) during a systemic rise of venous pressure produced by repeated Valsalva maneuvers. Though results varied slightly, depending on the method of calculation, representative filtration coefficients for the whole body were in the first 9.5 min, .0036 ml per min per 100 g body wt per cm rise of venous pressure and, for a total of 29.5 min, .0014. These values can be compared to .0033 and .0023 for the forearm alone. The two sets

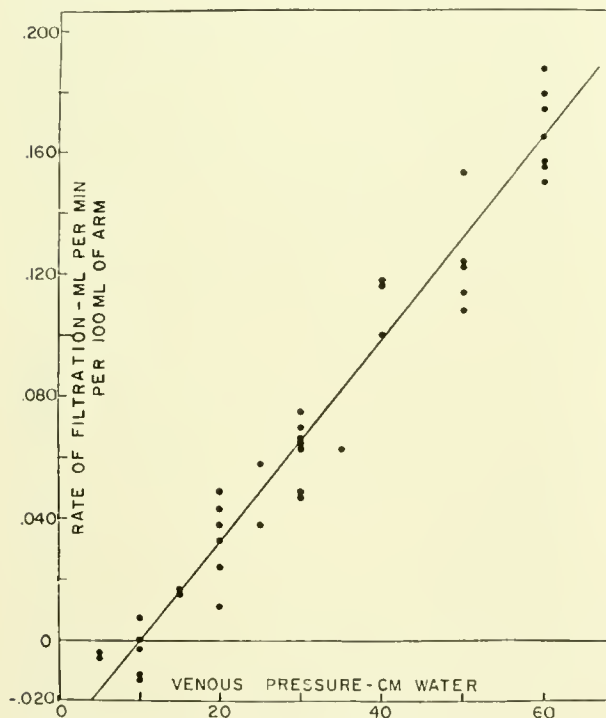


FIG. 6.2. Rates of filtration measured by pressure plethysmograph in human forearm during graded elevation of venous pressure for 10-min periods. Plethysmograph temperature, 34–35 C. The slope of the line corresponds to a filtration coefficient (k_f) of .0033 ml/min/100 ml forearm tissue per cm H_2O increase of venous pressure. [From Landis & Gibbon (209).]

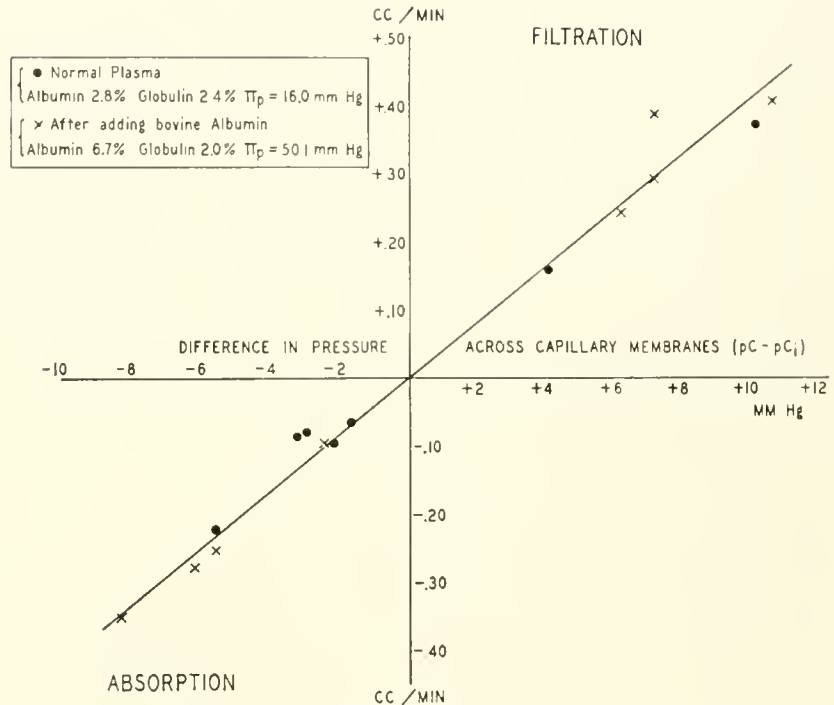
of figures are similar, presumably because the collective capillary beds of muscle and subcutaneous tissue are large compared to the smaller, though more permeable, capillary beds of liver and intestine. A similar relationship has been found with respect to diffusion (see section 8). The “whole body” filtration rate appears to decline more rapidly than that of the forearm, owing probably to more rapid return of capillary filtrate by way of the lymphatics, particularly during the vigorous respiratory movements required for repeated, brief Valsalva maneuvers.

Landis & Hortenstine (210) calculated from the forearm filtration figures (188, 209) that a rise of venous pressure, throughout the body, to 10 cm water above normal might, in a man weighing 75 kg, filter as much as 250 ml of fluid from the plasma in the first 10 min. This has proved a fairly good estimate. Brown *et al.* (22) observed the filtration of 333 ml to 501 ml when systemic venous pressure was elevated by 20 cm for 9.5 min. Over 29.5 min an increase of venous pressure by 20 cm water filtered 460, 417, and 687 ml of fluid, calculated to contain between 1 and 2 g of protein per 100 ml owing, presumably, in part to the very high protein content of capillary filtrate from hepatic and intestinal capillaries.

The pressure plethysmograph was used by Krogh *et al.* (188) also to test the effect on filtration rate of changing the osmotic pressure of the plasma proteins. Filtration rates at given venous pressures were measured with the subject recumbent and then at the same venous pressures while the subject stood quietly on a tilt table for 30 min or more. Quiet standing increased the concentration of the circulating plasma proteins by 0.6 to 1.1 g per 100 ml and the protein osmotic pressure of plasma by 3.3 to 8.7 cm water. At these higher protein osmotic pressures the rate of filtration produced by a given venous pressure was always lower. A unit rise of protein osmotic pressure (1 cm water) was accompanied by a reduction of filtration rate ranging from .0027 to .0045 ml per min per 100 ml forearm tissue. These values were quantitatively similar to the effect produced by elevating venous pressure by 1 cm water, but opposite in sign. Within the limitations of the method these results justified extending the Starling hypothesis to the forearm capillaries of man, and were compatible with the view that the capillaries of the human forearm were relatively impermeable to the plasma proteins.

In the first studies with the pressure plethysmograph (188, 209) it was perplexing to find that venous

FIG. 6.3. Relation of net fluid movement in perfused hind leg of cat to difference between the mean hydrostatic pressure in the capillaries (p_c) and the sum of all pressures opposing filtration (isogravimetric capillary pressure, p_{ci}). The slope of the line corresponds to a filtration coefficient (k_t) of 0.014 ml/min/100 g tissue/mm Hg pressure difference. [From Pappenheimer & Soto-Rivera (282).]



pressure had to be elevated by 10 to 17 cm water before net filtration could be detected (fig. 6.2). Brown *et al.* (24) showed later, however, that the regression lines relating filtration and venous pressure passed through zero, provided *a*) that interstitial fluid was carefully evacuated from the forearm prior to congestion, and *b*) that a correction was made for the volume of interstitial fluid pressed out of the forearm segment during each volume measurement.

From regression lines such as the one shown in figure 6.2 it is possible to calculate an approximate filtration coefficient (k_t) for forearm tissue if allowance is made for the fact that a given elevation of venous pressure produces a somewhat smaller elevation of mean capillary pressure. On the assumption that the latter is 80 per cent of the former, k_t for human forearm capillaries becomes approximately .0057 ml per min per 100 g tissue per mm Hg as given in table 6.2. The filtration coefficient for the whole body becomes .0061.

Among the several perfusion methods that have been used to measure filtration coefficients, the most precise and revealing is the isogravimetric technique developed by Pappenheimer & Soto-Rivera (282) in which filtration and absorption were identified by changes in weight of an isolated limb. Arterial pressure, venous pressure, osmotic pressure of the perfusing fluid, blood flow, and temperature could be varied at will and their influence on the filtration-

absorption equilibrium could be measured separately. A detectable effect on fluid movement resulted from a change of venous pressure by 0.5 mm Hg and sometimes less, or from a change of arterial pressure by 2 to 4 mm Hg. Capillary pressure was 5 to 10 times more sensitive to a change of venous pressure than to a change of arterial pressure.

Figure 6.3 shows net fluid movement, i.e., filtration or absorption, plotted against the difference in pressure across the capillary membranes themselves. Filtration and absorption were proportional to the difference between the calculated mean capillary blood pressure and the isogravimetric capillary pressure which is, by definition in this method, the sum of all pressures opposing filtration. In figure 6.3 the slope of the regression line indicates a filtration coefficient of .0105 ml per 100 g tissue per min per mm Hg change of capillary blood pressure. The filtration coefficient was independent of the absolute value of the isogravimetric capillary pressure when this was varied by diluting or concentrating the proteins in the perfusing fluid. Similar methods have been applied recently by Renkin & Zaun (302) to the hind legs of the rat.

The constancy of filtration coefficients at high and low capillary blood pressures (figs. 6.1, 6.2, 6.3) suggest that under these conditions capillary surface area and capillary porosity are not significantly modified by pressure. This may be related to the con-

clusions reached by Burton (31) that vessels of small diameter are relatively indistensible. Under more severe conditions and in other tissues, however, the permeability of the capillary walls may be increased when capillary blood pressures are very high (211) or when blood volume is much increased (131, 331, 361, 369).

In all the regions so far considered, resting average capillary blood pressure is approximately equal to the osmotic pressure of the plasma proteins. In the lung, however, as described in section 2, average capillary pressure is only 5 to 10 mm Hg and therefore less than half the osmotic pressure of the plasma proteins. Figure 6.4 shows the rate of edema formation in the lungs of dogs plotted against left atrial pressure (132). In contrast to other tissues, net filtration and increase of interstitial fluid volume were not observed until, at atrial pressures of 25 to 30 mm Hg, pulmonary capillary pressure began to exceed the protein osmotic pressure of 25 mm Hg. Thereafter filtration increased linearly with left atrial pressure at a rate of 0.21 g of fluid per hour per mm Hg per g dry wt of lung tissue or 0.065 g per min per mm Hg per 100 g wet lung tissue. The relative "dryness" of lung tissue which is produced by a low capillary pressure is indicated by the absence of filtration between atrial pressures 0 and 23 mm Hg. This margin of dryness was reduced to half normal when the plasma protein concentration was decreased by plasmapheresis to an average of 47 per cent of the control protein concentration. Taken together, the

results shown in figures 6.1 to 6.4 permit concluding that in these four regions the net rates of filtration or absorption through the capillary walls depend upon the difference between hydrostatic and osmotic forces acting across the membrane. In view of this evidence the Starling hypothesis of 1896 (345) can fittingly be called now the Starling filtration-absorption principle.

Progress has gone beyond this qualitative stage, however, because the meaning of k , the filtration coefficient, has been expanded not only by numerical values for a number of capillary beds and membranes (tables 6.1 and 6.2) but also by more precise definition. Pappenheimer (276) called attention to the fact that the several different "filtration constants," "unit filtration rates," or "filtration coefficients" used by various authors can be related to the equation used by Darcy (62) to describe the viscous flow of fluids through inert porous or fibrous materials, viz.:

$$\dot{Q}_f = \frac{k A_m \Delta P}{\eta \Delta x} \quad (6.1)$$

where

\dot{Q}_f = quantity filtered per unit time

k = specific filtration constant of the porous material or membrane

A_m = area of membrane

ΔP = pressure difference across membrane (in capillaries $\Delta P = P_c - P_{if} - \Pi_{pl} + \Pi_{if}$)

Δx = path length through membrane (for capillaries usually assumed to be 0.3μ)

η = viscosity of filtrate

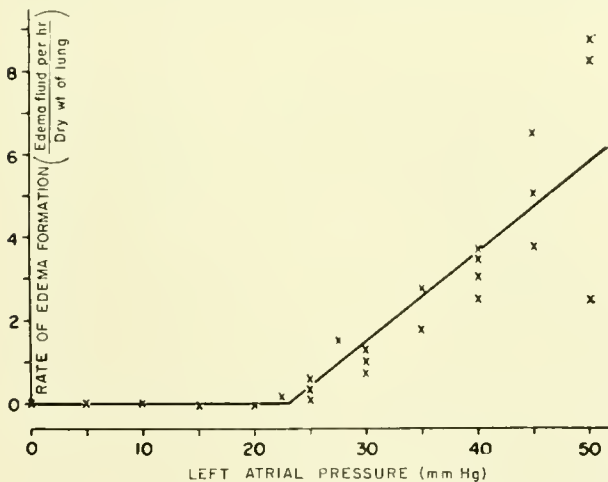


FIG. 6.4. Rate of edema formation (filtration) in lungs of dogs subjected to prolonged elevations of left atrial pressure. Significant filtration did not appear until left atrial pressure exceeded 25 mm Hg, i.e., the osmotic pressure of the plasma proteins. [From Guyton & Lindsey (132).]

If the area of capillary wall can be measured directly (23, 200, 201, 383) or computed (281, 282) as in table 6.1, the proportionality factor or filtration coefficient consists of $k/\eta\Delta x$ including the Darcy "specific filtration constant," the thickness of the wall, and viscosity of the fluid. On the other hand, for tissues in which the capillary surface per weight or volume of tissue is not yet known precisely, e.g., in the human forearm, the hind quarters of the rat, and the lung, the proportionality factor for unit tissue weight or volume will consist of $kA_c/\eta\Delta x$ including, in addition, the area of the capillary walls, A_c . The term "filtration constant" is certainly inappropriate and should be abandoned for a membrane system as heterogeneous as that in the capillary wall. Filtration coefficient is a preferable term and it is suggested that the symbol k_c be used for cases where the area of capillary wall is measured or computed and k_t be used for coefficients based on mass or volume of tissue. Newer developments in pore theory have led

TABLE 6.1. *Filtration Coefficients (Hydrodynamic Conductivity) Through Various Membranes**

| Type of Membrane | Temperature, C | Filtration Coefficient, ml sec \times cm ² \times cm H ₂ O $\times 10^8$ | References |
|-------------------------------------------------------|----------------|----------------------------------------------------------------------------------------------------------|-----------------|
| <i>Cell membranes</i> | | | |
| Arbacia egg (unfertilized) | 20 | 0.016 | (221, 222) |
| Fibroblasts (mouse, rat, chick) | 20-22 | 0.06-0.16 | (25) |
| Leucocytes (rabbit, man) | 20-23 | 0.05-0.2 | (329) |
| Erythrocytes (man) | 20 | 0.92 | (334) |
| <i>Capillary membranes</i> | | | |
| Muscle (dog, cat) | 37 | 2.5 | (281, 282) |
| Mesenteric (frog) | 22-26 | 48-74 | (23, 200, 201) |
| Glomerular (frog) | 25 | 220 | (281) |
| Glomerular (mammal) | 37 | 300-600 | (281, 276, 339) |
| <i>Artificial membranes†</i> | | | |
| Dialysis tubing (Visking) $r = 16-23 \text{ \AA}$ | 25 | 100-180 | (82, 298) |
| Cellophane (DuPont 450-PT-62) $r = 30-40 \text{ \AA}$ | 25 | 350-900 | (82, 298) |
| Viscose wet gel (Sylvania) $r = 75-85 \text{ \AA}$ | 25 | 3200-4200 | (82, 298) |

* Modified from Renkin & Pappenheimer (301). † Thickness, 0.5 μ , r = pore radius.

Pappenheimer (276) to suggest also that the term "capillary permeability" be reserved for describing the properties of the capillary wall with reference to the diffusion of small molecules. Filtration coefficients, because they deal with flow of fluid through a membrane, would then be a measure of hydraulic or hydrodynamic conductivity of the capillary wall.

Table 6.1 is taken from the review by Renkin & Pappenheimer (301) with inclusion of some more recent values. It compares filtration coefficients of cell membranes (upper section), of capillary walls (middle section), and of certain artificial membranes (lower section). Cell membranes have smaller filtration coefficients than capillaries, although the difference between the values for the erythrocyte and the mammalian muscle capillary is small. The range of filtration coefficients for capillary walls is very large, amounting to a 200-fold difference in the mammal between muscle capillaries and glomerular capillaries. The coefficients for artificial membranes, calculated for comparable thickness, are in turn much higher still and, with other evidence, led Pappenheimer *et al.* (281) to the conclusion that the collective area of the pores involved in the filtration process is only a small fraction of the total capillary surface. Support for this conclusion came from measurements of capillary permeability to small lipid-insoluble molecules, and will be given in sections 8 to 10.

Table 6.2 compares average filtration coefficients (k_t) for extremities of four species. In the forearm of

TABLE 6.2. *Average Filtration Coefficients for Tissues, k_t*

| Species and Tissue | Filtration Coefficient at 37 C, ml min \times 100 g tissue \times mm Hg | Reference |
|-------------------------|--------------------------------------------------------------------------------------|------------|
| | | |
| Man, forearm, intact | 0.0057* | (188, 209) |
| Man, whole body, intact | 0.0061* | (22) |
| Dog, perfused hind leg | 0.014 | (282) |
| Cat, perfused hind leg | 0.0105 | (281, 282) |
| Rat, perfused hind legs | 0.033 | (302) |

* In the text these coefficients are described for a rise of venous pressure by 1 cm water. To facilitate comparison, values given here have been corrected to 1 mm Hg rise of capillary pressure. It is assumed that $\Delta P_c = 0.8 \Delta P_v$.

man, on the assumption that capillary pressure is increased by 80 per cent of given increases in venous pressure, the average filtration coefficient becomes .0057 ml per min per mm Hg per 100 g tissue. From the data of Brown *et al.* (22) k_t for the whole body is .0061. In smaller animals progressively larger filtration coefficients are found. As Renkin & Pappenheimer suggest (301), this relationship is teleologically fitting because the smaller the mammal, the more active are its metabolic processes and therefore the greater will be the requirement for a more extensive capillary bed (320) and for more rapid exchanges between blood and tissue. To obtain comparable filtration coefficients for other tissues, e.g., liver, intestine, lung, and brain, is far more difficult. Values for lung have been published recently by Guyton & Lindsey (132) and for brain, or perhaps chiefly the arachnoidea, by Coulter (47).

B. Effects of Temperature on Filtration Coefficients

As noted above, the Darcy equation indicates that flow through porous materials changes with temperature in inverse proportion to viscosity, and accurate measurements of flow through artificial, porous membranes have confirmed this expectation (16, 81). The filtration coefficients for capillaries, k_c , and for tissues, k_t , include the viscosity of the filtered fluid and should change with temperature. This was found to be clearly the case by Pappenheimer (277) in the perfused limb in which the capillary membranes retain their normal impermeability to plasma proteins over a temperature range of 8 to 44 C. The ratio of the filtration coefficient measured at 36 ± 2 C to that measured at 10 ± 2 C averaged 1.68 ($SE = \pm 0.08$). This value was within 10 per cent of the ratio of viscosities of water at the two temperatures ($\eta_{10} / \eta_{36} = 1.85$) and the difference between the two ratios was not significant ($P > .05$).

In the frog mesentery Brown & Landis (23) had observed earlier a decrease of filtration coefficient (k_c) from .0070 to .0019 when temperature was reduced from 24 ± 2 C to 0 ± 2 C. However, as mentioned by Pappenheimer (276), the decrease in filtration coefficient was larger than that to be expected theoretically and the scatter of values for individual capillaries was too great for quantitative conclusions.

In the human forearm, Landis & Gibbon (209)

found the filtration coefficient (k_t) almost halved as the temperature of the plethysmograph (and of the superficial tissues of the forearm) was changed from 44 or 45 C to 14 or 15 C. Brown *et al.* (24) extended these observations to 4 to 5 C. Figure 6.5 (heavy line) shows the filtration coefficients observed in the forearm at plethysmograph temperatures over the total range of 44 to 4 C. Using the data of Barcroft & Edholm (9), the figures just above the bottom line of the chart show the probable temperatures in muscle and subcutaneous tissues corresponding to each surface temperature. Starting from the filtration coefficient at a tissue temperature of 35 to 36 C (surface temperature 34 to 35 C) the fainter, dash lines indicate coefficients of filtration calculated on the basis of deep tissue temperature and the corresponding change in viscosity of capillary filtrate. Observed and calculated filtration coefficients agree fairly well at tissue temperatures ranging from 35 to 17 C. Above 35 C the observed coefficient is much higher than the calculated one, indicating that changes other than viscosity are involved. To be considered are such factors as increased capillary pressure and filtering area (8) secondary to vasodilatation or, possibly, opening of arteriovenous anastomoses with elevation of small vein pressure. Below a tissue temperature of 17 C, the observed filtration coefficient does not decrease as it should if viscosity alone were involved, but in-

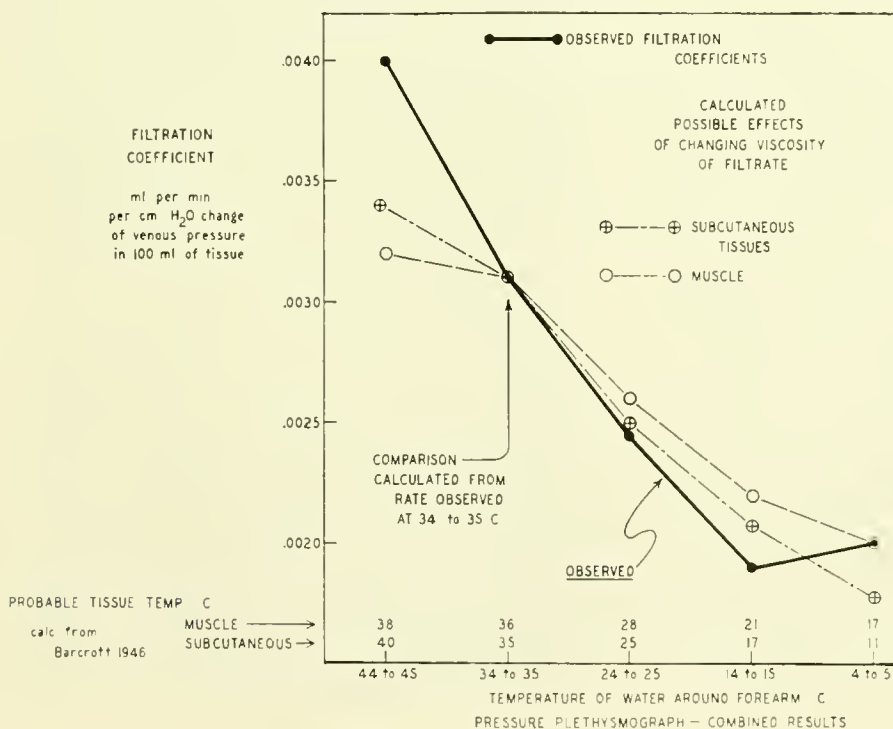


FIG. 6.5. Effects of temperature on filtration coefficients, k_t , observed in the human forearm (solid line), compared with filtration coefficients to be expected by calculation from change of viscosity of water by reason of temperature changes in muscle (---) and subcutaneous tissue (---) [Calculated from results of Landis & Gibbon (209), Brown *et al.* (24) and, for deep temperatures, Barcroft & Edholm (9).]

creases considerably. Moreover, Brown *et al.* (24) found that even at normal venous pressures cooling the surface of the forearm to 4°C produced a slow but steady increase of the reduced forearm volume presumably because of filtration and augmented interstitial fluid volume. These results suggested "cold injury" of surface capillaries and diminished effective osmotic pressure of the plasma proteins. Passage of protein through the capillary wall in severe cold has been described by Lewis (218), who found up to 3 g per cent of protein in the edema fluid. In summary, it appears that for intact tissues the effects of moderate changes of temperature on filtration coefficients can be explained fairly well by the changing viscosity of capillary filtrate. At very high and very low temperatures other factors, as yet unanalyzed, become more important.

C. Adsorbed Plasma Protein and Filtration Coefficients

The functional dimensions of capillary pores, and hence the filtration coefficients of capillaries, are probably determined in part, by a layer of adsorbed plasma protein. Krogh & Harrop (186) were the first to note that perfusion of extremities with non-protein colloids fails to prevent edema. Their observations were confirmed and extended by Drinker (74), Danielli (61), and Shleser & Freed (332). Kinter & Pappenheimer (cf table 6.3) found that dextrans failed to exert their full osmotic pressure in vivo unless more than 0.2 per cent protein was present in the perfusion fluid. Net filtration usually occurred in dextran-Ringer perfused muscle at all venous pressures; 10 to 20 min after addition of 1 per cent plasma protein the direction of net fluid movement was reversed as the osmotic pressure of the dextran became effective across the capillary walls. The phenomenon was fully reversible and could be repeated several times on the same preparation during the course of a few hours. The capillary filtration coefficient was usually more than doubled when Ringer's solution (295) or Ringer-dextran solutions were substituted for plasma. In nine experiments the filtration coefficient averaged $0.016 \pm .003$ ml per min per 100 g tissue during perfusion with blood, $0.037 \pm .002$ during perfusion with protein-free red cell suspensions, and $0.019 \pm .003$ when protein was restored to the perfusion fluid. The effect appears to be nonspecific, since normal filtration coefficients were found in cat or rat hind limbs perfused with human or bovine serum albumin (295), cat hemoglobin, or bovine hemoglobin (299).

TABLE 6.3. *Effective Osmotic Pressures of Clinical Dextran in Capillaries of Perfused Cat Hind Limbs*

| Perfusion Fluid | Effective Osmotic Pressure, mm Hg | |
|-------------------------------|-----------------------------------|-------------------------|
| | In vitro (Hepp osmometer) | In vivo (perfused limb) |
| <i>Experiment 1</i> | | |
| a) 3% Dextran | | |
| 2% Plasma protein in Ringer | 24.6 | 21.0 |
| b) 3% Dextran in Ringer | 22 | 6.6 |
| <i>Experiment 2</i> | | |
| a) 3% Dextran | | |
| 2.4% Plasma protein in Ringer | 30.8 | 28.5 |
| b) 3% Dextran | | |
| 0.2% Plasma protein in Ringer | 23.2 | 13.7 |
| <i>Experiment 3</i> | | |
| a) 3% Dextran in Ringer | 25.0 | 12.2 |
| b) 3% Dextran | | |
| 3% Plasma protein in Ringer | 31.4 | 26.4 |

From unpublished experiments of Kinter and Pappenheimer.

The minor axis of serum albumin is about 30 Å and complete removal of albumin from the inside of a pore might increase effective pore radius by this amount. Given a mean pore radius of 45 Å (see sections 9 and 10), the filtration coefficient would be expected to increase by the factor $(30 + 45)^4 \div (45)^4$ or more than sevenfold. A reversible increase of this magnitude was observed in only one preparation, but it is possible that even prolonged washout with protein-free solutions fails to remove all adsorbed protein. The effects of adsorbed protein should be considered, however, in comparing pore dimensions calculated from permeability measurements with pore dimensions observed in electron micrographs.

D. Effects of Injury on Filtration, Absorption, and Filtration Coefficients

CAPILLARY STASIS. Cohnheim in 1867 postulated a "molecular alteration in the vessel walls" and augmented "porousness" to explain the transudation of fluid, protein, and cells in inflammation (42, 43). Since then abundant qualitative evidence has indicated that injury of many types increases the permeability of the capillary wall to fluid and protein (207). Inflammation is, however, an exceedingly complex series of reactions (246, 247, 344), of which increased capillary permeability is only one part. Physiologists have, therefore, tended to study simpler forms of

injury. A few quantitative measurements in terms of filtration coefficients are available and provide estimates of the increased porousness even though information on the "molecular alterations" of the vessel walls is still completely lacking.

In considering the mechanism of simple, chemical injury, Krogh & Harrop (187) in 1921 described "capillary stasis" as direct microscopic evidence of increased permeability of the capillary wall. The steps by which chemical injury leads to capillary stasis merit full description, because capillary pressure, flow, filtration, absorption, and diffusion are all affected. The changes observed in a single, damaged capillary form a unit lesion which helps to explain the effects of more generalized injury.

Blood corpuscles, when first entering a capillary, are clearly separated by plasma. As long as the capillary wall is normal this remains the case and flow continues. Even when capillary blood pressure is high, filtration reduces the volume of plasma in flowing capillary blood very slightly, because the fraction of plasma filtered is normally less than 4 per cent of the plasma volume at most, and usually 1 to 2 per cent. However, as soon as injury is produced, e.g., by applying 25 per cent urethan or 10 per cent alcohol in Ringer's solution, the corpuscles clearly begin to move closer together as they flow along the capillary, because plasma is lost progressively through the now injured capillary wall. Eventually, at the venous end of the capillary, nearly all the plasma having been filtered off, the corpuscles become so closely packed, and collectively so viscous, that they come to a standstill in the capillary and form a localized plug of cells just short of the venule. Meanwhile plasma, with few or many erythrocytes, continues to enter the arteriolar end of the capillary, though much more slowly than before and in a distinctly pulsatile fashion, because entry is now limited by the volume of plasma being filtered through the damaged capillary wall.

The plasma of this blood is also lost by rapid filtration. The additional corpuscles are progressively concentrated in their turn and finally deposited cumulatively on the already existing column of erythrocytes in the venous end of the capillary. Eventually a column of packed cells fills the whole capillary and takes on a characteristic, transparent, bright red color, apparently because the erythrocytes are so closely packed that light rays are no longer refracted as they are when the surfaces of single corpuscles are normally separated by intervening plasma. Flow ceases entirely in capillaries thus filled and plugged.

If injury is severe, capillary stasis is irreversible. If

injury is mild, resumption of flow is frequently observed. The first indication of beginning recovery is the loosening of corpuscles in the packed column, followed by slow, then more rapid, squeezing of the column into the stream of the nearest venous capillary or venule. Here the cells can be seen separating easily in the plasma of the venules as they are carried away. In this respect simple stasis differs from the "sludged" corpuscles described by Knisely *et al.* (176) for more drastic states in which the corpuscles adhere to each other and form minute emboli.

Even after flow has returned some erythrocytes and leukocytes usually remain adherent to the inner surface of the damaged wall, but eventually these, too, float free (199). Platelets may be seen adhering to the wall for still longer periods and probably help restore relative impermeability to protein as suggested by Danielli's perfusion studies (61) in which platelets reduced the rate of edema formation to one-tenth that found with platelet-free perfusion media. Platelet protein, in association with calcium, has also been found to restore normal permeability (381).

Chemical injury of the grade just described increases capillary permeability enough to permit passage of plasma proteins (200), colloidal dyes (107, 152, 184, 199), and colloidal starch (184) but, as observed by light microscope, the walls of true capillaries still retain most of the carbon particles of injected India ink (152, 184, 199). This is true also of localized mechanical injury produced by compressing capillaries with a glass rod (199), or by prodding with a minute needle (37). In these simpler forms of injury gross ruptures of the capillary wall are not present because carbon particles, as well as erythrocytes, are retained as plasma is filtered off.

FILTRATION COEFFICIENTS, k_c , OF INJURED CAPILLARIES.

The permeability of injured capillaries has been measured in the frog's mesentery by determining their filtration coefficient during stasis using the method already described for normal capillaries (200). Figure 6.6 shows filtration rates plotted against capillary blood pressure, injury having been produced by irrigating the mesentery with 10 per cent alcohol or 1:10,000 mercuric chloride in Ringer's fluid. As with the normal capillary wall, filtration increased linearly with capillary blood pressure. Comparison of the regression lines for injured capillaries (above) and normal capillaries (below) indicates, however, that the filtration coefficient was

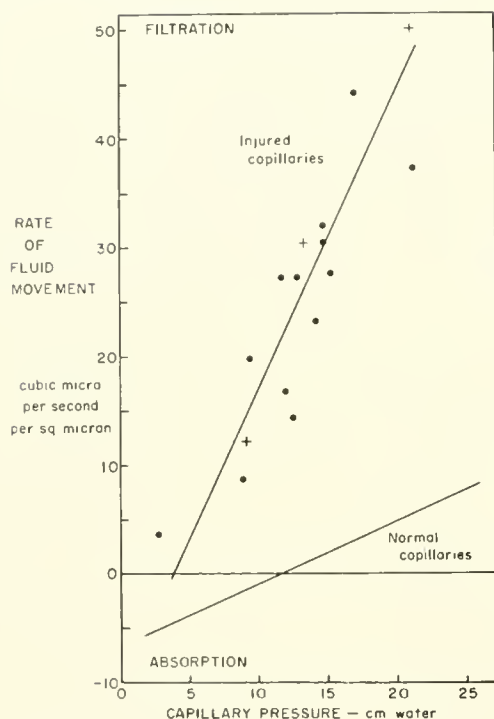


FIG. 6.6. Effects of severe chemical injury on fluid movement through walls of frog's mesenteric capillaries. Slope of lower regression line shows filtration coefficient, k_c , for normal capillaries. Slope of upper regression line indicates the 7-fold increase of filtration coefficient found after injury. Filled circles refer to injury by 10% alcohol in Ringer's fluid; plus signs, to 1:10,000 mercuric chloride in Ringer's fluid. [From Landis (200).]

increased from the normal value of 0.0056 to approximately $0.0390 \mu^3$ per sec per μ^2 of capillary wall per cm water of capillary pressure, indicating a sevenfold increase of hydrodynamic conductivity. Increased permeability of the injured wall to plasma proteins is indicated by the absence of absorption even at low capillary pressures and by the reduction of the *in vivo* osmotic pressure of the plasma proteins from the normal value of 11 cm water to between 3 and 4 cm water. Thus the effects of severe injury are *a*) increased filtration, *b*) absence of absorption, *c*) reduced effective osmotic pressure of the plasma proteins, and *d*) eventual cessation of flow in any capillary injured to the point of stasis. Diffusion rates have not been measured in such capillaries. Presumably, since capillary permeability to fluid and protein is greater, net diffusion of small molecules should be increased as long as blood flow continues. However, since net diffusion is flow limited, its effectiveness in exchanges of substances will decline as flow decreases and will

soon cease in those capillaries that are filled with stationary, closely packed erythrocytes.

CAPILLARY PRESSURE IN INJURY. The appearance of edema in injured regions is due primarily to increased capillary permeability, but is enhanced by increased capillary blood pressure. Local injury elevates capillary blood pressure by at least two mechanisms: 1) the vasodilatation and increased blood flow which are parts of the triple response to injury described by Lewis (217), and 2) the temporary blockage of capillary blood flow and passive congestion produced by stasis (199).

Application of a minute silver nitrate crystal to the skin of the frog's web increases capillary pressure in the neighborhood of the lesion to peak values which are as much as double the earlier control values (205). Within 10 to 20 min capillary pressure is again within the normal range. In human skin the flare of the triple response produced by histamine is accompanied by peak capillary pressures of 10 to 25 mm Hg above preceding control values (203), but again with relatively prompt return to control values. The onset and duration of these elevations suggest that they are a part of the flare due to the "axon reflex."

Elevations of capillary blood pressure are also found in capillaries injured to the point of stasis. These elevations are more important in the formation of edema fluid during injury because they occur in vessels, the walls of which are permeable to protein and hence already the site of rapid filtration without any balancing absorption. Figure 6.7 shows the cycle of pressure changes which occurred in one experiment involving stasis and recovery. Control capillary blood pressure, with normal blood flow, ranged from 12 to 15 cm water. At the time marked *A* 25 per cent urethan was applied to the mesentery and the onset of stasis, as indicated by visible loss of plasma, was clearly present at *B*. The sharp rise of capillary pressure between *B* and *C* occurred as the venous end of the capillary was filled and blocked by packed erythrocytes. As flow ceased capillary pressure rose rapidly to approach the pressure in the feeding arteriole. At *C* a pressure of 22.5 cm water merely stopped the advance of erythrocytes toward the pipette. Even 30 cm water did not move the corpuscles away so that capillary blood pressure was well in excess of the 22.5 cm water charted. The very rapid filtration observed during this period is due, therefore, to increased permeability and also to high capillary pressure. Between *C* and *D* this enhanced filtration of whole plasma packed erythrocytes

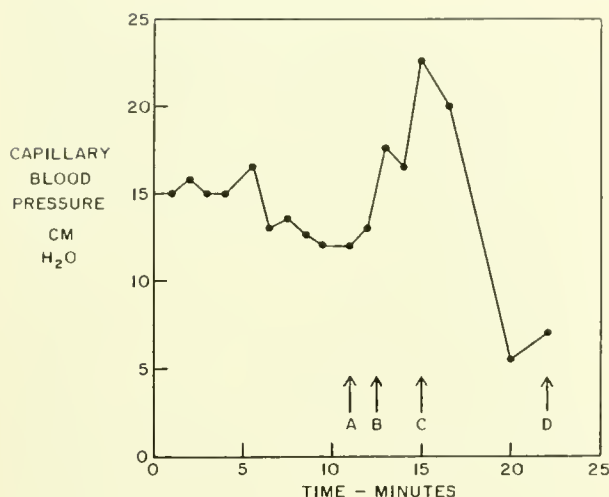


FIG. 6.7. Chart indicating the changes of capillary blood pressure in frog's mesentery during capillary stasis produced by applying 25% urethan solution (A to C) and during recovery with resumption of capillary blood flow (C to D). [From Landis (199).]

tightly throughout the capillary. After D, arteriolar pressure having been blocked by the packing of erythrocytes up to the arteriocalillary junction, capillary blood pressure fell to the level in the venule. This secondary fall of pressure seems to assist recovery from stasis because, as it occurs, one can observe that the erythrocytes become less tightly packed and slow movement toward the nearest venule begins. At D sluggish flow was being resumed. Hence in injury, capillary stasis and the rapid accumulation of relatively large volumes of protein-containing edema fluid or blister fluid depend primarily upon increased permeability, but also upon increased capillary blood pressure. Recovery from stasis, while assisted by temporary lowering of capillary blood pressure, cannot occur until the permeability of the wall to protein returns toward normal.

TISSUE ASPHYXIA; RELATION OF FILTRATION COEFFICIENTS TO O_2 , CO_2 , AND pH. The effects of arrested blood flow and, more specifically, of hypoxia on capillary permeability and the filtration-absorption mechanism are still uncertain. In general, it appears that arrest of blood flow must be total and prolonged, and that hypoxia must be severe, before changes in permeability become demonstrable. Lazarus-Barlow (213) in 1894 studied the edema of passive congestion, and also the edema which appeared when blood flow was restored after a prior period of complete arterial and venous occlusion. He ascribed the latter edema

to functional modification of the vessel walls secondary to "starvation of the tissues" and accumulated waste products. More recently Pochin (285) found in the rabbit's ear that occluding the circulation for 2 hours led to demonstrable edema which appeared shortly after circulation was re-established. Occlusions of 16 to 18 hours produced enough edema fluid to permit collecting samples in which the protein content approached 5 g per cent. Edema alone might conceivably have been the result of vasodilatation and high capillary blood pressure that probably followed this arrest of the circulation, but the high concentration of protein in the edema fluid indicated that increased permeability was also present.

Among the factors that might change capillary permeability under these conditions, the first to be considered are those associated with continued metabolism of tissues in the absence of blood flow, viz. a) reduced oxygen tension, b) increased carbon dioxide tension, and c) local decrease of pH due to accumulation of metabolites such as lactic acid. Table 6.4 summarizes the effects of these variables on the filtration coefficients (k_f) and on the in vivo effective osmotic pressures of the plasma proteins measured in single mesenteric capillaries of the frog (201). They indicate that Ringer's solution, saturated with CO_2 or acidified by HCl to pH's between 7.0 and 5.0, had no significant effect on the permeability of the capillary wall. Only when pH was made 4.0 or less, and hence unphysiologically low, was there evidence of increased permeability to fluid and protein.

Severe and, so far as possible, total oxygen lack made the capillary wall permeable to protein and fluid as indicated by decreased effective osmotic pressure of the plasma proteins and by increased filtration coefficient, respectively. It must be emphasized that the lowering of O_2 tension in these experiments was maximal because not only was blood flow stopped by tightening a loop around the mesenteric artery, but the mesentery was also irrigated freely with Ringer's solution previously boiled and kept saturated with nitrogen. The possibility that metabolites from anaerobic metabolism were responsible could not be excluded. The effects on permeability were, however, still reversible because, if the period of severe hypoxia was brief enough, e.g., 3 min, resumption of blood flow and irrigation with oxygenated Ringer's solution restored both the filtration coefficient and the in vivo osmotic pressure of the plasma proteins toward normal, as shown in table 6.4. For comparison, at the bottom of table 6.4

TABLE 6.4. *Effects of CO₂, O₂, pH, and Severe Chemical Injury on Frog's Mesenteric Capillaries*

| Capillaries Irrigated by Ringer's Fluid with | Filtration Coefficient, k_f $\frac{\mu^3}{\text{sec} \times \mu^2 \times \text{cm H}_2\text{O}}$ | Effective Π_{pl} (in vivo) cm H ₂ O |
|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Usual aeration | .0048-.0074* | 8.6-11.7* |
| Saturated CO ₂ | .0088 | 11.8 |
| pH 8.0 | .0056 | 11.5 |
| HCl to pH 6.0 | .0065 | 11.7 |
| 5.0 | .0074 | 11.4 |
| 4.0 | .0152 | 11.6 |
| 3.5 | .0207 | 7.8 |
| 3.0 | rapid stasis | |
| O ₂ lack and arrested blood flow for 3 min | .0231 | 6.5 |
| After 15 min recovery | .0080 | 11.5 |
| 10% alcohol or mercuric chloride, 1:10,000 | .0390 | <4.0 |

* Accumulated control measurements (23, 200, 201).

is shown the still greater effect of chemical injury severe enough to produce irreversible capillary stasis.

In contrast to the effects of extreme local hypoxia just described, studies of graded hypoxemia have demonstrated that the capillary wall tolerates less severe grades of oxygen lack very well. In the human forearm, Henry *et al.* (150) found that oxygen tension of venous blood must be reduced to between 15 and 25 mm Hg before protein passage was increased above normal. This corresponds to an oxygen saturation of 15 to 25 per cent or an oxygen content of 4 to 6 vol per cent, assuming the blood has a normal hemoglobin content. The method used to measure protein passage was, however, indirect and the protein content of capillary filtrate varied widely.

DiPasquale & Schiller (70) and Hendley & Schiller (148) studied the effects of hypoxemia on the rate of edema formation in limbs of rats perfused with Krebs-Ringer solution containing 20 per cent washed red cells of dog and 0.33 per cent gelatin. When the oxygen content of the perfusing fluid was kept above 5 vol per cent, the rate of edema formation remained at the control level. Reducing oxygen content to between 0.88 and 2.60 vol per cent increased the rate of edema formation above control levels by 42 per cent in the first 20 min, by 87 per cent in the next 20 min, and by 151 per cent in the third 20-min period. Blood flow having been kept constant to exclude effects of the vasodilatation which accompanied this hypoxemia, they concluded that the critical level below which hypoxemia influences

the permeability of a capillary wall was probably about 2.6 vol per cent. No observations on protein passage were made. In further studies Hendley & Schiller (149) found, however, that either histaminic (Neo-Antergan) or adrenergic (Dibenzyliline) blockade eliminated these results on the basis either of specific blocking action or of hemodynamic effects, and the meaning of these studies therefore remains a challenging problem.

Systemic hypoxemia, within the range compatible with the life of the organism, has no certain effect on capillary permeability. Maurer (228, 229) and Warren & Drinker (367) found, in dogs, that breathing 8.0 to 11.5 per cent oxygen in nitrogen augmented the flow of lymph from the lungs and cervical region, increased the total amount of lymph protein collected in unit time, but decreased the concentration of protein in that lymph. Although an increase of capillary permeability was postulated, the decreased protein concentration in lymph, taken together with the studies of Courtice & Korner (53, 179) make it unlikely that permeability to protein was changed. In the human forearm McMichael & Morris (242) found that breathing 9.5 per cent oxygen did not increase filtration from capillaries during venous congestion. Moreover, in patients with generalized hypoxemia sufficient to impair cerebral function, Stead & Warren (351) observed no significant increase in the protein content of edema fluids collected from the extremities.

Only in agonal or antemortem stages of asphyxia (34) or anoxemia (160) is there some slight evidence of increased capillary permeability. In shock the possibility that generalized hypoxemia might increase capillary permeability has been considered on many occasions. Careful studies with labeled plasma proteins (45, 101, 102) have shown the expected rapid passage of protein through capillary walls locally in burned or crushed tissues. However, no abnormal passage through capillary walls elsewhere in the body has been found until just before death, again as an agonal or antemortem occurrence.

In view of the many uncertainties already mentioned it is important to note that Bayliss & Lunds-gaard (11) perfused isolated kidneys with cyanide-containing blood and found that some tubular functions were reduced conspicuously, but that the glomerular capillaries and membranes remained nevertheless normally impermeable to protein in the two instances tested. In an earlier study Starling & Verney (348) found that the urine contained only a trace of protein after 15 min of cyanide perfusion,

though stepwise increases of proteinuria occurred after that. Pappenheimer found (unpublished studies) in the perfused cat's leg by the isogravimetric method that cyanide did not, under certain conditions, increase either the filtration coefficient or the permeability of the capillary wall to protein. This raises the interesting possibility that any effects which severe hypoxia may have on capillary permeability do not involve the better known cyanide-sensitive oxidations, but involve rather the 2 to 50 per cent (71, 224) of tissue oxygen consumption which cyanide does not inhibit even in high concentration. It is possible, too, that the edema of prolonged ischemia arises from the effects of anaerobically produced metabolic products or from other substances liberated by hypoxic tissue cells. In summary, the effects on capillary permeability of arrested blood flow, and more specifically of hypoxia, are still uncertain and require more careful studies both as to quantitative aspects and as to mechanism.

ADRENAL CORTICAL HORMONES AND FILTRATION COEFFICIENTS. Adrenal hormones have frequently been considered to be a factor in maintaining filtration coefficients and capillary permeability within normal limits even after injury. Menkin (245) and others (110, 332) observed that adrenal extracts and some adrenal steroids inhibited or delayed the appearance of intravenously administered trypan blue in the skin of rabbits where leukotaxine (110, 245) or peptone (332) had been injected locally. Some blanching of the skin was observed in the area treated with adrenal cortical hormones (110, 332), suggesting possible vasoconstriction. Hyman & Chambers (163) found in the perfused hind legs of frogs that the rate of edema formation was reduced by addition of certain adrenal cortical extracts to the perfusing fluid, but their method, like the preceding ones, did not exclude possible changes in capillary blood pressure.

Renkin & Zaun (302) applied to this problem the isogravimetric perfusion method of Pappenheimer & Soto-Rivera (282) which permitted measurement of *a*) filtration coefficients to indicate permeability to fluid and protein, *b*) osmotic transients to indicate permeability to small molecules, and *c*) blood flow to identify vasoconstriction. Addition of adrenal cortical extracts to both normal and adrenalectomized preparations produced vasoconstriction which was shown to be due to the presence of small amounts of an easily oxidizable substance, presumably epinephrine. Limbs from adrenalectomized animals

showed no increase of capillary permeability to protein and filtration coefficients for fluid did not differ significantly from normal. Addition of adrenal cortical extracts to the perfusing fluid produced slight decreases of the filtration coefficient, but evidence of vasoconstriction was also present. The addition of epinephrine to the perfusing fluid in amounts similar to that contaminating the extract produced corresponding changes, both of resistance to flow and of filtration coefficient. Permeability of the capillary wall to sucrose was also normal in adrenalectomized rats and was not affected by aqueous adrenal cortical extract.

The lack of agreement concerning the effects of adrenal extracts and steroids emphasizes again (208) the necessity for devising methods which separate a direct action of substances on capillary permeability per se from the indirect effects of complicating vasodilatation or vasoconstriction. Vasodilatation can increase capillary blood pressure; thus favoring greater filtration through an unchanged capillary wall. Conversely, vasoconstriction can reduce capillary blood flow and pressure, and also the area of capillary wall available for diffusion and filtration. Such hemodynamic changes will, of themselves, modify exchanges of substances, and thus simulate a change of permeability. The quantitative measurement of increases or decreases of capillary permeability is still one of the most difficult problems in physiology.

POROSITY OF THE INJURED CAPILLARY WALL. The effect of injury on the size of possible pores in the capillary wall was considered by Krogh (184) in 1922. From the passage of soluble starch and the retention of carbon particles he concluded that pore diameter was not less than 50 Å nor more than 2000 Å. For normal limb capillaries of cats the present corrected estimate for mean effective pore diameter lies between 80 and 90 Å (see sections 8 to 10). If it be assumed *a*) that injury merely enlarges existing pores, and *b*) that Poiseuille's equation holds for filtration through these pores, then a sevenfold increase of filtration coefficient can be explained by a 65 per cent increase of pore diameter, i.e., from the normal 80 to 90 Å up to between 130 and 150 Å. Judging from the effects of reduced pH shown in table 6.4 a doubling of filtration coefficient does not increase protein passage measurably, whereas a threefold to fourfold increase does. It may be, however, that injury increases the size or number of the larger openings postulated by Grotte (126) and by

Mayerson *et al.* (232) or that ultramicroscopic disruption of vessel architecture produces new and still larger apertures. Electron microscopy has shown recently, for instance, that histamine can produce separation of endothelial cells in venules so that carbon particles pass between endothelial cells to rest against the basement membrane (226, 226a). Additional evidence in favor of enlarged leaks or of new openings in injury has been provided recently by Courtice & Morris (50-52, 54). Concentrations of total cholesterol and of phospholipids were studied in order to determine the plasma to lymph gradients of lipoproteins in the limbs of cats and rabbits before and after injury. These gradients were compared with those for albumin and globulins. In lymph from normal legs the concentrations of albumin, globulins, cholesterol, and phospholipids were, respectively, 48, 35, 24, and 33 per cent of the plasma levels. After thermal injury the corresponding figures for lymph were 81, 74, 60, and 74 per cent of the plasma levels. Increased permeability to protein was accompanied by increased permeability to lipoproteins, the diameters of which have been placed tentatively at 150 to 350 Å (144). Larger fat particles, measuring perhaps 1500 Å or more, e.g., the particles in chyle or in an artificial fat emulsion, were not transferred through the capillary wall to lymph to any measurable extent, even after injury. However, as Courtice mentions (52), although the passage of lipoproteins and lipids becomes less as the size of the molecule or complex increases, the exact mechanism of their passage, whether between or through endothelial cells, is still obscure. In addition, the molecular mechanism and ultramicroscopic location of capillary damage may well differ, depending upon the type of injurious agent involved (208). Hence the basic nature of Cohnheim's "molecular alteration in the vessel walls" in various types of injury remains still a prime unknown requiring study by pathologists, physiologists, and electron microscopists alike.

7. DIFFUSION, GENERAL PRINCIPLES

The extravascular circulation caused by capillary filtration and absorption is exceedingly important for homeostasis of blood volume and for removal of large protein molecules via the lymphatics. However, the magnitude of the extravascular circulation is too small to be of significance for the metabolic exchange of small molecules between blood and tissues (see fig. 5.2). Metabolic exchange takes place largely by diffusion processes which are almost independent of the magnitude and direction of net fluid movement.

Evidence to be discussed below indicates that diffusion of lipid-insoluble molecules takes place through aqueous channels between capillary endothelial cells. Lipid-soluble molecules, on the other hand, diffuse rapidly through the lipid plasma membranes of the endothelial cells themselves and are thus free to utilize the entire capillary surface area for the exchange process. Before undertaking a detailed analysis of diffusion processes in the capillary circulation, it will be helpful to review some physical laws governing molecular diffusion in free solution and in simple membranes.

A. Free Diffusion

The fundamental laws of free diffusion were first described by Fick (96) in 1855.

Adolf Fick (1829-1901) was Professor of Physiology in Würzburg. His most numerous publications were in the field of muscle physiology, but his several classical contributions to science were in the form of short, single publications in unrelated fields. Among circulatory physiologists he is known chiefly as the originator of the "Fick principle" for determination of cardiac output. Among ophthalmologists he is noted for the development of tonometry and as author of "Fick's law" relating deformation of the cornea to intraocular pressure. It is probable, however, that his greatest contribution to science was his clear formulation of the laws of diffusion based on analogy with Fourier's description of the flow of heat. "Die Verbreitung eines gelösten Körpers in Lösungsmittel geht, sofern sie ungestört unter dem ausschliesslichen Einfluss der Molecularkräfte stattfindet, nach demselben Gesetze vor sich, welches Fourier für die Verbreitung der Wärme in einem Leiter aufgestellt hat. . . Man darf nur in dem Fourier'schen Gesetz das Wort Wärmemenge mit dem Worte Quantität des gelösten Körpers, und das Wort Temperatur mit Lösungsdichtigkeit vertauschen."

According to Fick's formulation, the rate of linear diffusion (quantity, n , per unit time, t) in direction x and through cross-sectional area, A , is proportional to the concentration gradient, dc/dx .

$$dn/dt = D A dc/dx \quad (7.1)$$

The constant of proportionality, D , is known as the diffusion coefficient and its dimensions are l^2t^{-1} . The simplest possible application of equation 7.1 is to steady-state diffusion where dc/dt is constant as a function of both distance and time. In this case, the equation 7.1 can be written

$$\dot{n} = D A \Delta c / \Delta x \quad (7.2)$$

where the concentration gradient $\Delta c / \Delta x$ is constant all along the diffusion path. Equation 7.2 is specially applicable to diffusion through thin membranes where the concentrations on the two sides of the

membrane can be maintained constant. This condition is frequently encountered in the capillary circulation where blood on the luminal side of the capillary membrane is maintained at constant composition by virtue of an adequate blood flow and fluid on the tissue side of the capillary membrane is maintained at a different constant composition as a result of tissue metabolism. A specific example will serve to illustrate the use of equation 7.2 and at the same time indicate the magnitude of diffusion in systems of capillary dimensions. Consider the diffusion of glucose across an aqueous boundary .5 μ (0.5×10^{-4} cm) thick and with a surface area of 10 cm². The diffusion coefficient of glucose is 0.9×10^{-5} cm² per sec (see table 9.1). Let the concentration of glucose on one side of the boundary be maintained constant at 100 mg per cent and the concentration on the other side of the boundary at 99 mg per cent, thus producing a constant concentration difference of 0.01 mg per cm³. Substituting these values in equation 7.2, we have

$$\begin{aligned} \dot{n} &= .9 \times 10^{-5} \frac{\text{cm}^2}{\text{sec}} \times 10 \text{ cm}^2 \times \frac{.01 \text{ mg/cm}^3}{0.5 \times 10^{-4} \text{ cm}} \\ &= 0.018 \text{ mg/sec or } 1.08 \text{ mg/min} \end{aligned}$$

This rate of transfer is greater than the normal metabolic consumption of glucose in 100 g of skeletal muscle containing more than 5,000 cm² of total capillary surface and it is thus obvious that even a small concentration difference operating over a relatively small aqueous area will provide a physiologically sufficient diffusion flow of glucose through distances comparable in thickness with the capillary wall.

Fick realized that the driving force for diffusion results from random kinetic motions of the diffusing molecules, but he did not perceive the physical significance of the diffusion coefficient. It remained for Nernst (1888) to relate diffusion coefficient to osmotic and frictional forces in solution (260). Nernst showed that

$$D = RT/fN \quad (7.3)$$

where f is the frictional force opposing unit linear velocity of each molecule and N is the number of molecules per mole (Avogadro's number). For the case of large spherical molecules the frictional force opposing diffusion is given by Stokes' law describing the motion of a sphere falling at unit velocity in a viscous medium

$$f = 6\pi\eta a \quad (7.4)$$

where η is the viscosity of the medium and a is the molecular radius. In 1905 Sutherland (355) and Einstein (91) independently noted the possibility of combining equations 7.3 and 7.4 to obtain the relationship between free diffusion coefficient and molecular radius

$$D = RT/6\pi\eta a N \quad (7.5)$$

Equation 7.5 indicates that diffusion coefficient is inversely related to molecular radius and to the viscosity of the diffusion medium; conversely the equation allows calculation of molecular radius from measurements of free diffusion coefficient. It should perhaps be emphasized that molecules are rarely spherical and the molecular radius calculated from the Einstein-Stokes relation (equation 7.5) is a virtual quantity represented by a sphere of equivalent diffusion coefficient. Moreover, the equation is derived on the assumption that the diffusing molecules are large compared to the solvent molecules; for molecules smaller than glucose it is necessary to apply corrections such as those given by Gierer & Wirz (116). Additional methods for estimating molecular dimensions include calculations from density, intrinsic viscosity, and X-ray diffraction data. Table 9.1, based on more detailed tables published in references 82, 281, and 298, shows free diffusion coefficients and approximate molecular radii of a variety of molecular species which have been used in studies of capillary permeability.

B. Diffusion Through Porous Membranes, Restricted Diffusion

The diffusion of small molecules through thin, large-pored membranes takes place according to Fick's law; the only effect of the membrane is to reduce the total area available for free diffusion. Indeed, the most accurate method of estimating the pore area, A_p , in a membrane with large water-filled pores is to measure the diffusion rate, \dot{n} , through the membrane of small, uncharged molecules of known free diffusion coefficient. From rearrangement of Fick's law

$$A_p = \dot{n} \times \frac{\Delta x}{D\Delta c}$$

In most practical applications the path length, Δx , through the membrane is also unknown and it is more useful to solve for the pore area per unit path length, $A_p/\Delta x$

$$\frac{A_p}{\Delta x} = \frac{\dot{n}}{D \Delta c} \quad (7.6)$$

Once the pore area per unit path length, $A_p / \Delta x$, has been established from equation 7.6 for a given large-pored membrane, the membrane may be used to determine free diffusion coefficients of test molecules (233, 264, 316). Membranes employed for this purpose generally have pores which are at least 100-fold larger than the diffusing molecules.

In the case of diffusion through membranes having pores of molecular dimensions the kinetic motions of the diffusing molecules are restricted by the pore structure; in such membranes the effective pore area per unit path length decreases as a function of molecular size, becoming zero when the test molecules are the same size as the pores. Capillary permeability to lipid-insoluble molecules of graded sizes can be explained, in large part, by restricted diffusion through aqueous channels of molecular dimension. For this reason it will be necessary to discuss physical aspects of restricted diffusion in some detail.

Figure 7.1 shows apparent pore areas per unit path length for molecules of graded sizes diffusing through a cellulose membrane of the type commonly used for ultrafiltration or dialysis (Visking sausage casing). It is evident that the apparent pore area for free diffusion decreases rapidly as a function of molecular size. The true pore area in the membrane is, of course, constant and it is useful to think of the apparent decrease in terms of a restricted diffusion coefficient, D' , such that

$$D' = D A_s / A_p \quad (7.7)$$

where A_s is the apparent pore area for the solute and A_p is the true pore area. Substitution of D' for D in equation 7.6 would yield the true membrane pore area per unit path length for all molecular species. The essential theoretical problem is now to relate the observed restriction to diffusion, D'/D , to dimensions of the membrane pores.

The theory of restricted diffusion proposed by Pappenheimer *et al.* (281) takes into account two factors impeding the passage of molecules through pores of molecular dimensions. The first factor is concerned with steric hindrance at the entrance of the pore. It is assumed that for entrance into a pore a molecule must pass through the opening without striking the edge as originally suggested by Ferry (95). For the case of cylindrical pores the effective target area, A_s , for the solute is then

$$A_s = A_p (1 - a/r)^2 \quad (7.7a)$$

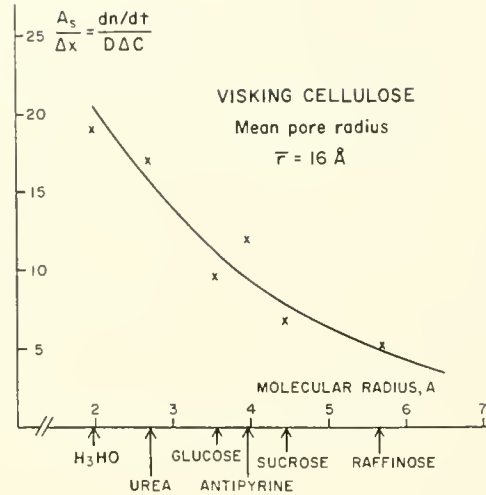


FIG. 7.1. Apparent pore areas per unit path length as a function of molecular size. The smooth curve is constructed from the theory of restricted diffusion, equation 7.9, assuming a mean pore radius of 16 Å. Mean pore radius determined on the same membrane from combination of diffusion and filtration was 19 Å (equation 7.13). Similar data for diffusion of lipid insoluble molecules through the walls of muscle capillaries are shown in figure 9.2. [Adapted from Renkin (298).]

where A_p is the true geometrical area of the opening and a/r is the ratio of molecular radius to pore radius.

The second factor takes account of friction between a molecule moving within a pore and the stationary walls of the pore. This factor, first studied by Ladenburg (193), was employed by Friedman & Kraemer (112) to describe the diffusion of sugars through gelatin gels. The Ladenburg treatment of the problem is strictly applicable only to cases where $a/r < .1$ and it is preferable to use the more general formulation of Faxén (94)

$$\frac{f}{f_0} = 1 - 2.10 \left(\frac{a}{r}\right) + 2.09 \left(\frac{a}{r}\right)^3 - 0.95 \left(\frac{a}{r}\right)^5 \quad (7.8)$$

where f/f_0 is the frictional resistance to diffusion in the pore relative to that in free solution. Taking into account both steric hindrance (equation 7.7a) and wall effects (equation 7.8), the theoretical restriction to diffusion through cylindrical pores becomes

$$\frac{A_s}{A_p} = \frac{D'}{D} = \left(1 - \frac{a}{r}\right)^2 \left[1 - 2.10 \left(\frac{a}{r}\right) + 2.09 \left(\frac{a}{r}\right)^3 - 0.95 \left(\frac{a}{r}\right)^5\right] \quad (7.9)$$

The last term of the series is negligible when $a/r < 0.5$. During net flow through the membrane the

velocity of flow at the center of the pore is twice the average velocity and the effective target area presented by the pore to the incoming molecules is slightly increased (95). Under these conditions the restricted diffusion equation becomes

$$\left(\frac{A_s}{A_p}\right)_{flow} = \left[2\left(1 - \frac{a}{r}\right)^2 - \left(1 - \frac{a}{r}\right)^4\right] \left[1 - 2.10\left(\frac{a}{r}\right) + 2.09\left(\frac{a}{r}\right)^3 - 0.95\left(\frac{a}{r}\right)^5\right] \quad (7.10)$$

Figure 7.2 shows that equation 7.9 describes observed diffusion through artificial porous membranes with considerable accuracy. The data were obtained using seven molecular species and three membranes having porosities in the range of interest for capillary physiology. Analogous development of theory for restriction to diffusion through rectangular slits, rather than cylindrical pores, leads to a theoretical curve closely approximating that shown in figure 7.2 (281). However, electron micrographs indicate that true pore geometry of artificial membranes is closer to the cylindrical than to the rectangular model (27).

Study of figure 7.2 reveals that pores of sufficient size to allow the slow penetration of plasma proteins (i.e., 30–40 Å) will nevertheless impose differential restriction to diffusion of much smaller molecules. Thus diffusion of glucose ($a = 3.7$ Å) through pores of radius 40 Å will be slowed by 34 per cent, whereas diffusion of water through the same pores will be slowed by only 14 per cent. This differential restriction to diffusion of small solutes and water is the

essential factor underlying transcapillary fluid shifts caused by transient changes in the concentration of small molecules in either plasma or tissue fluids.

The theory of restricted diffusion provides a method for estimation of effective pore radius, both in artificial membranes and in living capillaries. Thus equation 7.9 contains only two unknowns, D' and r , and it is therefore possible to solve for r from observed diffusion rates of two molecular species of known free diffusion coefficients and molecular radii. Greater accuracy can be obtained from the best fit of equation 7.9 to results obtained from several molecular species as shown in figure 7.1. Pore dimensions calculated from the theory of restricted diffusion agree well with values obtained by independent methods (298).

C. Diffusion and Hydrodynamic Flow, Relation to Pore Dimensions

Hydrostatic or osmotic forces, acting across a porous membrane, cause net fluid movement in proportion to the difference between hydrostatic and effective osmotic pressure (equation 1.1). Two different mechanisms are involved, diffusion and hydrodynamic flow.

DIFFUSION. The effective concentration (thermodynamic activity) of water depends upon pressure, temperature, and solute concentration. An increase of pressure or temperature increases the kinetic energy of the water molecules and therefore increases the statistical probability of net movement toward a region of lower pressure or temperature. Conversely, the addition of solute molecules to water decreases the probability of net diffusion of water to a region of lower solute concentration. For an ideal semipermeable membrane Fick's law may be restated as follows to take account of these variables

$$\frac{dn_{H_2O}}{dt} = \frac{\dot{q}}{\bar{V}_{H_2O}} = D_{H_2O} \frac{A_p}{\Delta x} \left(\frac{\Delta P - \Delta \Pi}{RT} \right) \quad (7.11)$$

where \dot{q} is rate of net water flow (ml/sec) and \bar{V}_{H_2O} is the partial molal volume of water (18 cm³/mole). The term $(\Delta p - \Delta \Pi)/RT$ replaces the concentration term in Fick's law and represents the difference in activity of water molecules on the two sides of the membrane. Formal derivations of equation 7.11 may be found in references (38) or (170).

HYDRODYNAMIC FLOW. The minimum dissipation of energy for net water flow through a membrane

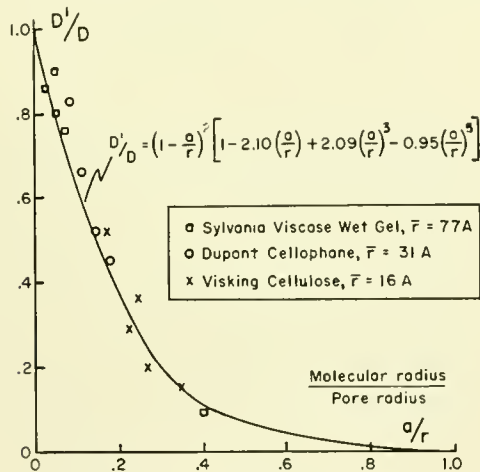


FIG. 7.2. Restricted diffusion through artificial porous membranes of various pore sizes. The smooth curve is drawn from the theory of restricted diffusion, equation 7.9. [Adapted from Renkin (298).]

containing N cylindrical pores of radius r will occur if the velocity profile assumes the parabolic distribution of Poiseuille's law.

$$\begin{aligned}\dot{Q} &= \frac{N\pi r^4}{8\eta \Delta x} (\Delta P - \Delta \Pi) \\ &= \frac{A_p}{\Delta x} \frac{r^2}{8\eta} (\Delta P - \Delta \Pi)\end{aligned}\quad (7.12)$$

Equation 7.12 implies that hydrodynamic streaming occurs even when the hydrostatic pressure difference across the membrane is zero, i.e., during flow caused by purely osmotic forces. The question is often raised as to how Poiseuille flow could occur in the apparent absence of a difference in hydrostatic pressure. An explanation of this apparent paradox was first offered in an important paper by Schlögl (317) who pointed out that a hydrostatic pressure drop accounting for hydrodynamic flow does indeed exist along most of the length of the membrane pores, even though the hydrostatic pressures on the two sides of the membrane are equal. The intra-membrane hydrostatic pressure gradient reverses sharply near the edge of the pore where it becomes equal and opposite to the steep gradient of diffusion potential. A more detailed treatment of this hypothesis will be found in the recent paper by Ray (292).

Comparison of equation 7.11 with equation 7.12 reveals that for a given total pore area, A_p , net flow by diffusion is independent of pore radius, whereas hydrodynamic flow varies with the second power of the pore radius. It follows that for a given difference in hydrostatic pressure the hydrodynamic component of flow will increase rapidly as a function of pore size. Figure 7.3 shows the relative importance of diffusion and hydrodynamic flow as a function of pore radius. For porosities in the range of interest for capillary permeability (e.g., 20–50 Å) the hydrodynamic component of net flow is overwhelmingly greater than the diffusion component. The capillary filtration coefficient discussed in section 6 is therefore a measure of hydrodynamic conductivity rather than diffusion permeability. Detailed discussions of the relations between diffusion permeability and hydrodynamic conductivity will be found in papers by Koefoed-Johnson & Ussing (177), Pappenheimer (276, 277), Garby (113), Durbin *et al.* (83) Kedem & Katchalsky (170) Katchalsky (169), Mauro (230), and Ray (292). A recent experimental evaluation of diffusion and hydrodynamic flow through artificial membranes has been published by Robbins & Mauro (303).

Combination of diffusion data with hydrodynamic

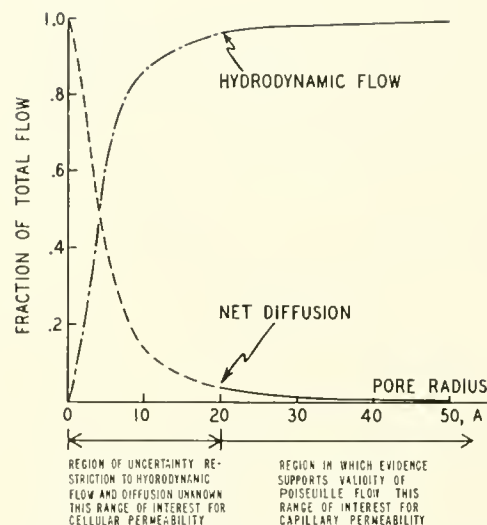


FIG. 7.3. Net diffusion and hydrodynamic flow of water as a function of pore size during flow induced by hydrostatic or osmotic forces. For membranes with effective pore radii greater than about 20 Å the net flow of water by diffusion is negligible compared to hydrodynamic flow. [From Pappenheimer (276).]

data leads to a solution for pore dimensions. Equation 7.11 describing hydrodynamic or osmotic flow through cylindrical pores can be rearranged to give

$$r = \sqrt{\frac{\dot{Q}_f}{(\Delta P - \Delta \Pi)} \times \frac{8\eta}{A_w/\Delta x}}$$

But $\dot{Q}/(\Delta P - \Delta \Pi)$ is the filtration coefficient defined by equation 1.1 and $(A_w/\Delta x)$ can be determined from diffusion of labeled water as shown in figure 7.1. Therefore, the effective pore radius is defined by measurable quantities

$$r = \sqrt{\frac{8\eta K_f}{A_w/\Delta x}} \quad (7.13)$$

Similar equations, based on diffusion and hydrodynamic flow, can be derived to estimate the dimensions of slit pores (18, 281) or any other pore geometry for which the laws of hydrodynamic flow are known.

Equation 7.13 has been used to estimate pore size in artificial membranes (82, 298) and in living capillaries (281). In general there is good agreement between pore size estimated from flow and diffusion and pore size estimated from restricted diffusion (fig. 7.1).

D. Simultaneous Flow and Restricted Diffusion: Theory of Molecular Sieving

In the capillary circulation both filtration and restricted diffusion usually occur simultaneously and

these two processes, operating together, are largely responsible for observed concentrations of large molecules in lymph (126) and renal glomerular filtrate (194, 278, 366). From the theory of molecular sieving described below it is possible to make deductions concerning capillary permeability for comparison with results obtained by independent methods. The degree of molecular sieving of a given solute may be defined as the ratio of its concentration in the filtrate (c_2) to its concentration in the filtrand (c_1). It is often supposed that during ultrafiltration of a monodisperse solute through an isoporous membrane, the value of c_2/c_1 will be zero when the pores are smaller than the solute molecules and unity when the pores are larger than the solute molecules. If intermediate values are actually observed they are said to be evidence for heteroporosity. If, for example, the concentration of a given solute in a capillary ultrafiltrate is 50 per cent of that in plasma it is supposed that half the capillary pores were smaller than the solute molecules and half were larger (21, 208, 232, 254). This reasoning fails to explain the dependence of molecular sieving on filtration rate. The following considerations show that molecular sieving of a monodisperse solute through an isoporous membrane is determined by the ratio of restricted diffusion to rate of filtration.

If the passage of solute through a porous membrane is restricted relative to passage of solvent, then the

$$\frac{c_2}{c_1} = \frac{1 + \frac{D_s}{\dot{Q}_f} \times \frac{A_w}{\Delta x}}{\frac{\left[2\left(1 - \frac{a_w}{r}\right)^2 - \left(1 - \frac{a_w}{r}\right)^4\right] \left[1 - 2.10\left(\frac{a_w}{r}\right) + 2.09\left(\frac{a_w}{r}\right)^3 - 0.95\left(\frac{a_w}{r}\right)^5\right]}{\left[2\left(1 - \frac{a_s}{r}\right)^2 - \left(1 - \frac{a_s}{r}\right)^4\right] \left[1 - 2.10\left(\frac{a_s}{r}\right) + 2.09\left(\frac{a_s}{r}\right)^3 - 0.95\left(\frac{a_s}{r}\right)^5\right]} + \frac{D_s}{\dot{Q}_f} \times \frac{A_w}{\Delta x}} \quad (7.15)$$

filtrate will be diluted during filtration, thus giving rise to a concentration difference for diffusion at a rate determined by the restricted diffusion coefficient, D' , through the membrane. The ultimate steady-state composition of the filtrate relative to filtrand (c_2/c_1) is therefore determined by a race between hydrodynamic flow (\dot{Q}_f) tending to dilute the filtrate and restricted diffusion tending to restore the concentration difference. A quantitative expression for molecular sieving through isoporous membranes was derived by Pappenheimer (276)

$$\frac{c_2}{c_1} = \frac{1 + \frac{D_s}{\dot{Q}_f} \times \frac{A_w}{\Delta x}}{\frac{A_w}{A_s} + \frac{D_s}{\dot{Q}_f} \times \frac{A_w}{\Delta x}} \quad (7.14)$$

Inspection of equation 7.14 shows that at low rates of

filtration, c_2 approaches c_1 (dialysis) and at high rates of filtration c_2/c_1 approaches the ratio of restricted pore areas A_s/A_w . Equation 7.14 is derived on the assumption that the concentration gradient through the membrane is linear. Grotte (126), Garby (113), and Kuhn (192) have pointed out that the concentration gradient in the membrane will in general be an exponential function of flow velocity, but this correction was shown by Grotte to be a small one and will be neglected here.

The restricted pore areas, A_w and A_s , have been expressed by equation 7.10 as a function of molecular radius and pore radius. Substitution of this function in equation 7.14 yields a cumbersome but explicit expression for molecular sieving as a function of filtration rate when molecular and membrane pore dimensions are known; conversely, it provides an independent method for calculation of pore size from experimental measurements of molecular sieving and filtration rate.

Figure 7.4 shows experimentally determined values of molecular sieving as a function of filtration rate through Visking dialysis membrane. The theoretical curves were drawn according to equation 7.15, using the value of $A_w/\Delta x$ determined from diffusion of tritiated water and choosing pore radii to provide the best fits to the experimental data for each molecular species. Satisfactory fits were obtained with pore radii 15 to 17 Å. Pore radius for the same membrane estimated from the theory of restricted diffusion

(fig. 7.1) was 16 Å, and pore radius estimated from combination with Poiseuille's law was 19 Å (equation 7.13). The internal consistency of these various estimates of pore radius in artificial membranes constitutes the chief evidence justifying the application of similar techniques to biological membranes.

E. Distribution of Pore Sizes

Observed values for diffusion and molecular sieving through artificial porous membranes are in reasonable accord with theoretical predictions for isoporous membranes. Equal or slightly better agreement between experiment and theory can be obtained by assuming certain limited distributions of pore sizes (298). An upper limit to pore size may be determined

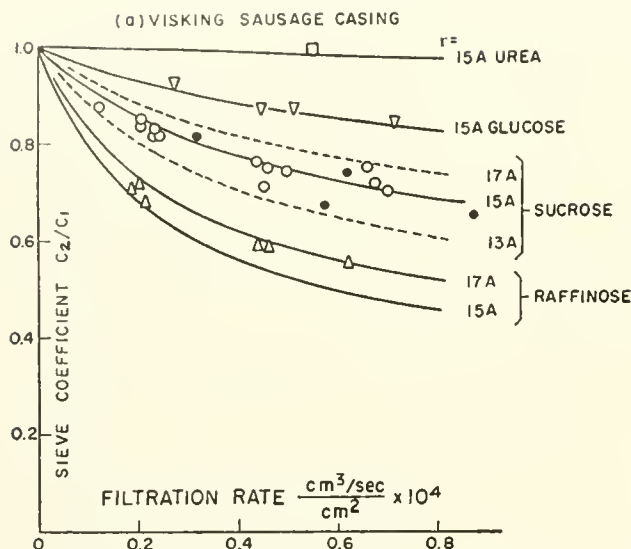


FIG. 7.4. Molecular sieving through an artificial, porous membrane. The smooth curves are constructed from the theory of molecular sieving, equation 7.15. The data fit pore radii in the range 15–17 Å. Mean pore radius for the same membrane estimated from the theory of restricted diffusion was 16 Å and pore radius estimated from combination with Poiseuille's law was 19 Å. The internal consistency of these various estimates of pore radius in artificial membranes constitutes the chief evidence justifying the application of similar techniques to biological membranes of comparable pore size. [Adapted from Renkin (298).]

from the size of the largest molecule which just fails to pass through the membrane. A less obvious limit to any assumed distribution arises from the fact that filtration rate varies with the fourth power of the radius so that the total fraction of large pores must be limited in order to satisfy the requirements imposed by the observed filtration coefficient. If a membrane contains cylindrical pores of different radii then the mean equivalent pore radius, \bar{r} , for hydrodynamic flow is given by

$$\bar{r} = \sqrt[4]{F_1 r_1^4 + F_2 r_2^4 + \cdots + F_n r_n^4} \quad (7.16)$$

where F_n is the fraction of total pore population having a radius r_n . For example, the membrane illustrated in figures 7.1 and 7.4 did not allow the passage of hemoglobin (a 32 Å) and therefore an upper limit to its pore size distribution is 32 Å. However, less than 20 per cent of the pores could be as large as 30 Å otherwise

$$\bar{r} > \sqrt[4]{0.2 \times (30)^4} > 20 \text{ Å}$$

which would not fit the requirement that $r = 19$ Å set by the observed filtration coefficient and diffusion

area for water (equation 7.13). The detailed computation of possible pore distributions which would fit the data for filtration, restricted diffusion and molecular sieving is possible but laborious. For the membrane illustrated in figures 7.1 and 7.4 the broadest Gaussian distribution of pore radii compatible with the data is defined by a mean pore radius of 14 Å with a standard deviation of 7 Å (298).

F. Osmotic Pressure³ and Osmotic Flow Through Leaky Membranes; Osmotic Reflection Coefficients

Van't Hoff's law relating osmotic pressure to concentration was derived for a perfectly semi-permeable membrane. Relatively little is known of osmotic forces associated with diffusion and osmotic flow through membranes which restrict, but do not prevent entirely, the diffusion of solute molecules. The quantitative significance of this problem may be illustrated by a specific example. Consider a two-compartment system separated by a membrane containing pores of radius 30 Å. Addition to one compartment of an ideal solute of molecular radius 30 Å will cause osmotic flow through the membrane at a rate equal to that caused by a hydrostatic pressure difference of cRT mm Hg (equation 7.12). However, if the same molar concentration of a small molecule such as urea (molecular radius 2.7 Å) is added to one compartment, it will be found that the osmotic flow is less than 5 per cent of that obtained by the hydrostatic equivalent (82).

In 1951 Staverman (349, 350) introduced the expression "osmotic reflection coefficient," σ , as an empirical descriptive term modifying van't Hoff's law for the case of leaky membranes.

$$\Pi = CRT\sigma \quad (7.17)$$

The value of σ ranges from unity in perfectly semi-permeable membranes to less than zero when the mobility of the solute exceeds that of the solvent (333).

Very small values of σ have been reported for osmotic flow caused by small molecules diffusing

³ "Osmotic pressure" is ordinarily defined for the case of thermodynamic equilibrium across ideal semipermeable membranes and the term has no equivalent meaning for the irreversible process to be considered here. Possibly a different term should be coined to describe the transmembrane pressures arising during restricted diffusion through porous membranes. "Restricted diffusion pressure" would be accurate but could only be applied to the case of zero net flow of solvent through the membrane.

through large pored artificial membranes. Thus Meschia & Setnikar (250) found that less than 2 per cent of the ideal osmotic potential was developed by sucrose during osmotic flow through a collodion membrane having pores of radius 110 Å (i.e., when the radius of the pore was approximately 25-fold greater than the radius of the diffusing molecule). Similarly low values for osmotic reflection coefficient have been reported by Grim (125) and by Shuler *et al.* (333) on the basis of osmotic flow through uncalibrated membranes.

Durbin (82) has recently completed a study of osmotic flow caused by molecules of graded sizes diffusing through calibrated porous membranes. His results shows that

$$\sigma \leq \left(1 - \frac{A_s}{A_w}\right)$$

where A_s is the restricted pore area available to the solute and A_w is the restricted pore area available to the solvent as defined by equation 7.9 and figure 7.1. Durbin's results indicate that during osmotic flow through artificial membranes the value of σ is less than 0.1 when the radius of the diffusing molecule is 10 per cent of the radius of the pore.

From existing data one must therefore conclude that only a small fraction of the theoretical van't Hoff pressure is operative across artificial membranes during restricted diffusion of small molecules through the membranes. On the other hand, relatively large osmotic forces have been observed during the restricted diffusion of small molecules through biological membranes under conditions involving little or no net fluid movement (122, 281). Under these conditions the osmotic reflection coefficient appears to depend upon the restricted diffusion coefficient of solute relative to that of the solvent.

$$\sigma = \left(1 - \frac{D'_s}{D'_w}\right) = \left(1 - \frac{A_s}{A_w} \times \frac{D_s}{D_w}\right) \quad (7.18)$$

Combination of equation 7.18 with equation 7.9 allows numerical evaluation of σ for the case of zero net fluid movement when molecular radius and pore radius are known. Thus,

$$\sigma_s = 1 - \frac{D_s}{D_w} \left\{ \frac{\left(1 - \frac{a_s}{r}\right)^2 \left[1 - 2.10\left(\frac{a_s}{r}\right) + 2.09\left(\frac{a_s}{r}\right)^3 - 0.95\left(\frac{a_s}{r}\right)^5\right]}{\left(1 - \frac{a_w}{r}\right)^2 \left[1 - 2.10\left(\frac{a_w}{r}\right) + 2.09\left(\frac{a_w}{r}\right)^3 - 0.95\left(\frac{a_w}{r}\right)^5\right]} \right\} \quad (7.19)$$

Equation 7.19 is specially applicable to capillary membranes where osmotic forces can be measured

rapidly in the virtual absence of net fluid movement (281).

In experiments involving artificial membranes it is exceedingly difficult to measure osmotic forces in the absence of osmotic flow, as pointed out in section 3. For this reason all investigations of osmotic reflection coefficient in artificial systems have thus far involved net flow of fluid. Under these conditions the frictional forces determining osmotic reflection coefficient will contain hydrodynamic as well as diffusional terms as emphasized in recent derivations by Ray (292) and Katchalsky (169). Discussion of these derivations is beyond the scope of this chapter but it seems fair to say that no well-substantiated theory is yet available to predict osmotic reflection coefficients as a function of membrane permeability and flow rate. Since most biological membranes allow the restricted passage of environmental solutes, the problem remains as one of the most important unsolved questions in contemporary studies of permeability.

8. TRANSCAPILLARY MOVEMENT OF LIPID-INSOLUBLE MOLECULES

The concentration gradients which provide the driving force for diffusion exchange between blood and tissues are normally maintained by tissue metabolism. However, the transcapillary exchange process is so efficient that normal transcapillary concentration differences of small molecules would be too small to be detectable by existing methods, even supposing it were feasible to collect, for analysis, tissue fluid from the immediate vicinity of the capillary wall. From an experimental point of view it is therefore necessary to establish abnormally large transcapillary concentration ratios in order to study diffusion characteristics of the capillary walls.

Figure 8.1 summarizes data showing rates of disappearance from the circulatory system of various lipid-insoluble substances which distribute primarily in extracellular fluid. It is evident that these substances leave the vascular system at rates which vary

inversely with molecular size. Disappearance from plasma is accompanied by simultaneous appearance

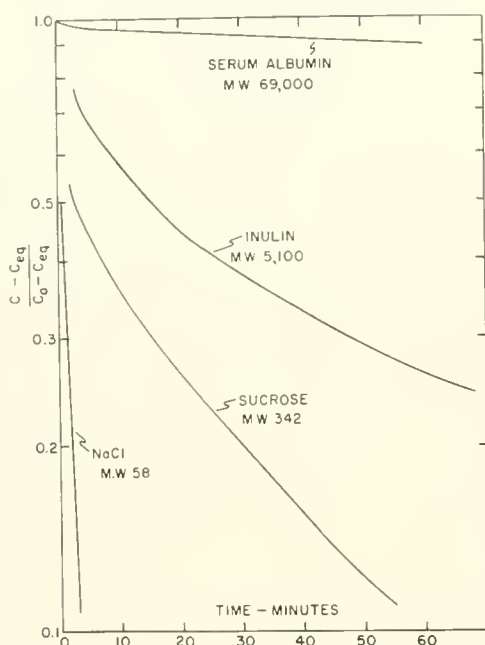


FIG. 8.1. Disappearance of substances from arterial plasma of rabbits. Data for albumin are from Gitlin *et al.* (118), data for inulin and sucrose are from Kruhoffer (190, 191), and data for NaCl are from Morel (257). C is concentration in arterial plasma at time t ; C_{eq} is concentration in plasma at equilibrium; C_0 is initial concentration in arterial plasma obtained by extrapolation to zero time.

of the test molecules in tissue spaces, again at rates which vary inversely with molecular size. Most tissues of the body participate in the distribution process, though at widely different rates.

The rapid penetration of capillary walls by molecules as large as sucrose or inulin implies a high order of permeability to lipid-insoluble molecules. Cell membranes generally (i.e., the plasma membranes which envelop the protoplasm of all living cells) are virtually impermeable to metabolically inert, lipid-insoluble molecules as large as sucrose; indeed they generally have a low order of permeability to most ions. The behavior illustrated in figure 8.1 is more characteristic of artificial porous membranes and this resemblance has given rise to the hypothesis that capillary blood communicates directly with extravascular fluid via a system of aqueous pores or channels. Recent studies of capillary ultrastructure (93) support earlier views (37, 276) that the structural basis for this type of permeability is associated with junctional regions between capillary endothelial cells. The number, dimensions, and properties of transcapillary pores which would be necessary to account

for observed capillary permeability to lipid-insoluble molecules will be considered more fully in section 9.

Initial experiments with isotopic tracers led to the suggestion that arterial disappearance curves might provide a quantitative measure of capillary permeability (106, 138). For this purpose it was assumed that diffusion from blood to extravascular space could be represented by a simple two-compartment diffusion system separated by the capillary membranes and that concentrations in each compartment would be uniform at each moment during the diffusion process. The theoretical equation describing diffusion in this simplified model is easily derived from Fick's law and leads to the expression

$$\lambda = - \frac{DA_s}{\Delta x} \frac{(V_1 + V_2)}{V_1 V_2} \quad (8.1)$$

where λ is the (negative) slope of the observed exponential disappearance curve, V_1 is plasma volume and V_2 is extravascular distribution volume (106, 233). Reference to equation 7.2 shows that the term $DA_s / \Delta x$ is the flux per unit concentration difference, $\dot{n} / \Delta c$, and is therefore a direct measure of capillary permeability to the test molecules. More complex equations describing arterial disappearance curves have been derived to take account of loss by the kidneys, loss by metabolism and distribution between more than two compartments in series or in parallel (318, 319, 330, 341, 363).

Equation 8.1 is specially applicable to the case of large, lipid-insoluble molecules such as proteins or synthetic polymers. Diffusion of such substances from the vascular system is so slow that their concentrations in arterial plasma may be taken as a close approximation of mean concentration in capillary plasma, i.e., the concentration gradient along the length of each capillary is negligible at all times during the diffusion process. In the example of figure 8.1 the slope, λ , for albumin is about -0.1 per cent of the initial concentration per min, or 100 per cent of the plasma albumin every 16.6 hours. Similar values for transcapillary exchange rates of serum albumin have been observed in dog (370) and man (352). The free diffusion coefficient of albumin is 0.085×10^{-5} cm² per sec. Given a normal plasma volume, V_1 , of 4 per cent of body weight and a normal extracellular fluid volume, V_2 , of 20 per cent then from equation 8.1 the effective capillary pore area per unit path length available for restricted diffusion of serum albumin is 65 cm per 100 g tissue. This value may be compared with the value of 70 cm per 100 g muscle calculated

from the theory of restricted diffusion through pores of radius 43 Å (table 9.1).

Arterial disappearance curves therefore provide a method for quantitative studies of overall capillary permeability to large molecules. It is not possible, however, to extend this type of analysis to molecules which diffuse rapidly through capillary walls. In this case the mean concentration in capillary plasma may be only a small fraction of that in arterial plasma, particularly in early phases of the distribution process. Application of equation 8.1 to such data leads to estimates of capillary permeability which are too low, often by 1 or 2 orders of magnitude [see (281) and (382) for critical review]. Factors which determine mean concentration differences of small molecules across capillary walls during diffusion include rate of blood flow, diffusion rate, and the geometry and volume of extravascular diffusion space. Several interesting attempts have been made to take account of these factors by mathematical techniques but the solutions are complex and involve assumptions which are difficult to evaluate experimentally (19, 319).

Specialized experimental methods for estimating capillary permeability to small molecules were developed by Pappenheimer *et al.* (281) for the study of molecular exchanges in the capillary circulation of hind limbs of cats or dogs. Results obtained by these methods lead to conclusions of general interest relating capillary permeability to the number and dimensions of capillary pores which would be required to explain observed transcapillary diffusion rates of lipid-insoluble molecules ranging in size from D₂O to hemoglobin.

9. STRUCTURE OF MUSCLE CAPILLARIES AS DEDUCED FROM PERMEABILITY MEASUREMENTS AND FROM ELECTRON MICROSCOPY. QUANTITATIVE ASPECTS OF TRANSCAPILLARY DIFFUSION

In isolated perfused tissues the rate of net transcapillary movement of test substances can be determined from the product of blood flow and arterio-venous concentration difference. Thus,

$$\dot{n} = Q(c_a - c_v) \quad (9.1)$$

where Q is blood (or plasma) flow and c_a , c_v are the simultaneously measured concentrations of the test substance in arterial and venous bloods (or plasma).

The driving force for diffusion (i.e., the mean concentration difference across the capillary walls) may be estimated from the partial osmotic pressure

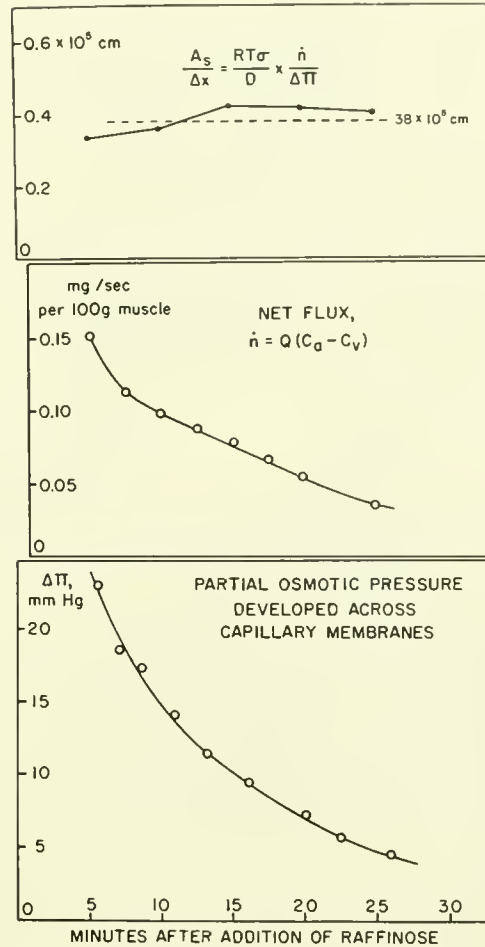


FIG. 9.1. Diffusion of raffinose from the capillaries of a perfused cat hind limb. At zero time 20 mm/liter raffinose was added to the perfusion reservoir. The final distribution volume of raffinose in perfused tissue was 19% of limb volume. The capillary diffusion area per unit path length calculated for raffinose was 0.38×10^5 cm²; this value was independent of time, extravascular fluid volume, or of mechanically induced changes of blood flow. [Adapted from Pappenheimer *et al.* (281).]

exerted by the test molecules during the diffusion process. Figure 9.1 illustrates a typical experiment showing the simultaneous measurement of net flux rate and partial osmotic pressure during the diffusion of raffinose from the capillaries of a perfused cat hind limb. The ratio of flux rate to partial osmotic pressure is proportional to permeability and may be related to the restricted pore area per unit path length in the capillary wall by combining equations 7.6 and 7.17.

$$\frac{A_s}{\Delta x} = \frac{RT\sigma_s}{D_s} \times \frac{\dot{n}}{\Delta \Pi} \quad (9.2)$$

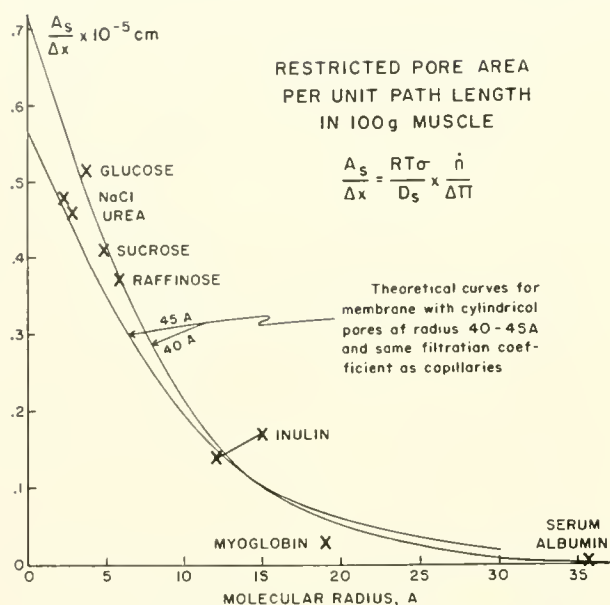


FIG. 9.2. Restricted diffusion of lipid-insoluble molecules from the capillaries of perfused cat hind limbs. Each point represents the mean value of data from several experiments. The curves are constructed from the theory of restricted diffusion and filtration (equation 9.3) on the assumption that the osmotic reflection coefficient is determined by equation 7.19. The data fit theoretical restricted diffusion through pores of radius 40–45 Å in a membrane having the same filtration coefficient as the capillaries in the hind limb. [Recalculated from the data of Pappenheimer *et al.* (281).]

The upper panel of figure 9.1 shows that for raffinose the restricted pore area per unit path

$$r^2 \left\{ \frac{\left(1 - \frac{a_w}{r}\right)^2 \left[1 - 2.10\left(\frac{a_w}{r}\right) + 2.09\left(\frac{a_w}{r}\right)^3 - 0.95\left(\frac{a_w}{r}\right)^5\right]}{\left(1 - \frac{a_s}{r}\right)^2 \left[1 - 2.10\left(\frac{a_s}{r}\right) + 2.09\left(\frac{a_s}{r}\right)^3 - 0.95\left(\frac{a_s}{r}\right)^5\right]} - \frac{D_s}{D_w} \right\} = \frac{8\eta K_f}{RTD_s} \times \frac{\Delta\pi}{\dot{n}} \quad (9.3)$$

length, calculated from equation 9.2, was $0.38 \pm .04 \times 10^5$ cm. Results of similar measurements, made with a variety of molecular species, are shown in figure 9.2. It is seen that in capillaries, as in artificial porous membranes (fig. 7.1), the restricted pore area decreased as a function of molecular radius as predicted from the theory of restricted diffusion (equation 7.9). Extrapolation to zero molecular radius suggests that the true pore area per unit path length in the capillaries of 100 g muscle is approximately 0.6×10^5 cm. Since the average thickness of the capillary walls is less than 10^{-4} cm (fig. 9.3), this suggests that the total pore area available for diffusion exchange of lipid-insoluble molecules is less than 6

cm² or less than 0.1 per cent of the total capillary surface area in 100 g muscle. This conclusion is consistent with the view that transepillary exchanges of lipid-insoluble molecules take place at junctional regions between endothelial cells and we have already seen that pore areas of this magnitude can provide a physiologically sufficient flow of small molecules under the influence of small concentration gradients (section 7 A).

In the original analysis of Pappenheimer *et al.* (281) the mean pore radius was estimated from combination of the capillary filtration coefficient with the pore area per unit path length for a molecule the size of water (equation 7.13). However, the latter quantity was uncorrected for the osmotic reflection coefficient and therefore cannot be employed for the present analysis in which the osmotic reflection coefficient is included as an unknown. In order to solve for this additional unknown it is necessary to introduce an additional equation relating osmotic reflection coefficient to pore dimensions as suggested by equation 7.19. This equation is cumbersome and its use may not be entirely justified on the basis of our present inadequate knowledge of factors determining osmotic reflection coefficients. Nevertheless, it leads to a solution for capillary pore dimensions which is more consistent with available data than the dimensions originally proposed by Pappenheimer *et al.* (281). Substitution of equations 7.19 and 9.2 in equation 7.13 yields

where

- r = mean capillary pore radius, Å
- a_w = radius of water molecule = 1.5 Å
- a_s = radius of test molecule, Å
- D_w = free diffusion coefficient of water = 3.4×10^{-5} cm² per sec⁻¹
- D_s = free diffusion coefficient of test molecule
- η = viscosity of water = 0.007 dyne-sec-cm⁻² at 37 C
- K_f = filtration coefficient of capillaries, average value 1.8×10^{-7} cm⁵-dyne⁻¹-sec⁻¹ per 100 g
- $\Delta\pi$ = observed partial osmotic pressure, dynes-cm⁻² at time, t
- \dot{n} = observed flux rate, mole-cm² at time, t
- RT = 25×10^9 dyne-cm-mol⁻¹ at 37 C

Study of equation 9.3 in relation to the experimental

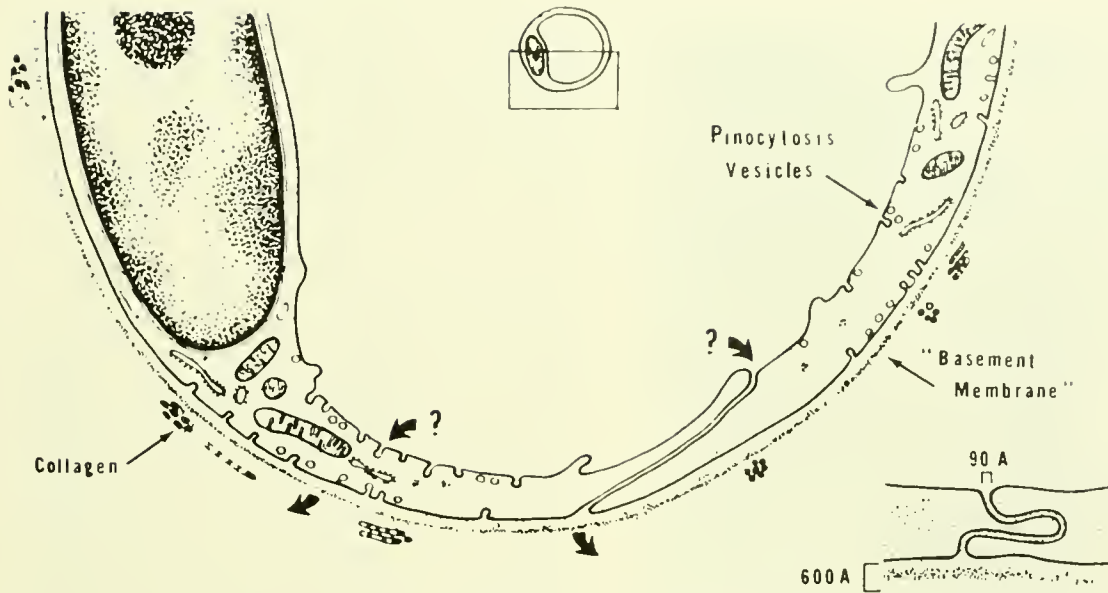


FIG. 9.3. Diagram illustrating current concepts of fine structure in muscle capillaries. [From Fawcett (93).] The nucleus of a single endothelial cell is shown at left. The capillary cross section may be formed by a single cell rolled into a tube or may be made up of several cells. The interendothelial region appears as a thin slit pore with direct connection from inside to outside of capillary. The slit may be straight or slightly tortuous (inset and fig. 9.4) and is usually about 90 Å wide and 0.5–1 μ in length. It occupies only a fraction of 1% of the total endothelial surface. The cytoplasm contains the usual organelles, but in addition contains numerous small vesicles and in-pocketings of the surface which are characteristic of microphagocytosis or pinocytosis. Palade (273) has suggested that this mechanism may be involved in the transcapillary passage of particles which are too large to traverse interendothelial openings. The outer surface of the endothelium is enveloped by an amorphous basement membrane about 600 Å in thickness and with histochemical properties indicative of a mucopolysaccharide. The permeability properties of this membrane are unknown. Dilute solutions of mucopolysaccharides, in contrast to gelatin-gels (112), may offer appreciable resistance to free diffusion (266). Finally, it should be emphasized that the diagram refers only to muscle capillaries. Morphological differences between capillaries in different vascular beds have been reviewed by Bennett *et al.* (13).

data of figure 9.2 reveals that the pore radius, r , is the only unknown quantity. The numerical evaluation of r from equation 9.3 may be carried out by successive approximation or by graphical analysis. For the specific example illustrated in figure 9.1 the value of r is 41 Å. Similar analysis of data for NaCl, urea, glucose, and sucrose leads to mean pore radii of 44, 43, 45, and 41 Å, respectively. These results are in accord with values in the range 35 to 45 Å estimated by Grotte (126) from molecular sieving of dextrans in hind limb capillaries (section 10 and fig. 10.1). They are in contrast to the value of 30 Å estimated by Pappenheimer *et al.* (281) from combination of filtration coefficient with uncorrected diffusion data and to the value of 25 Å estimated by Renkin & Pappenheimer (301) from uncorrected restriction to diffusion. The dimensions and fractional

surface area of aqueous transcapillary pores correspond closely with dimensions of interendothelial junctions as determined by electron microscopy. Figure 9.3 summarizes pertinent aspects of pore structure in muscle capillaries; details of a typical interendothelial junction are illustrated in figure 9.4. On the basis of present information we can compare the permeability of capillaries in 100 g of muscle to that of an artificial membrane, 7000 cm^2 in total area, 0.5 μ thick and containing 5×10^{12} uniform, water-filled, cylindrical pores of radius 40 to 45 Å. Such an artificial membrane would have the same filtration coefficient as the capillaries in 100 g muscle and would restrict the diffusion of uncharged, lipid-insoluble molecules to about the same degree (fig. 9.2). There are no reasons for supposing, however, that the channels through capillary walls are either

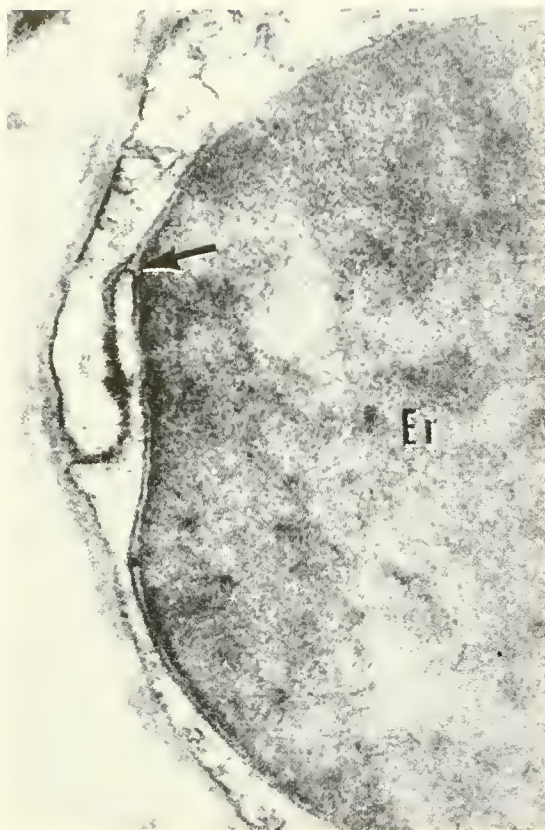


FIG. 9.4. A portion of the wall of a capillary (heart muscle) to show details of the interendothelial junction. The junction provides a continuous channel connecting the inside of the capillary with the outside basement membrane. The width of the channel is about 100 Å. The interior of the capillary is almost filled with an erythrocyte. [From Fawcett (93).]

cylindrical or perfectly uniform. Alternative models utilizing different pore geometries or a limited distribution of pore sizes could be devised to simulate observed capillary permeability. The significant fact is that both the hydrodynamic and diffusional characteristics of the capillaries can be explained in terms of a simple physical model which closely approximates the morphology of the capillary wall. The mean pore radius calculated as above may be regarded as analogous to the Einstein-Stokes molecular radius (equation 7.5) which by itself tells nothing of the actual shape of the molecule but is nevertheless valuable for predicting kinetic behavior.

The restricted pore areas shown in figure 9.2 represent only a minute fraction of the total capillary surface, but they nevertheless provide for extremely rapid transcapillary diffusion of small lipid-insoluble molecules. The pore area per unit path length avail-

able for diffusion of water through the capillary walls of 100 g muscle is about 0.6×10^5 cm (fig. 9.2). The concentration of water available for diffusion in either direction is about 55 molar (0.99 g/ml) and the diffusion coefficient of water is 3.4×10^5 cm² per sec. Substitution of these values in Fick's diffusion equation leads to a calculated diffusion rate of 2 g per sec. Since the total volume of plasma in the capillaries of 100 g of muscle is only about 1 ml, this suggests that plasma water exchanges 2 times per sec or 120 times per min with the interstitial water immediately surrounding the capillaries. Similar calculations for NaCl, urea, and glucose yield exchange rate of 60, 55, and 30 times the plasma content of these substances per minute. An alternative method of expressing the results is in terms of the ratio of exchange rate to plasma flow. The latter is generally in the range 2 to 4 ml per min per 100 g tissue. Taking 3 ml per min as an average, we would estimate that the diffusion of water, NaCl, urea, and glucose back and forth through the capillary wall occurs at rates which are, respectively, 40, 20, 18, and 10 times the rate at which these substances are brought to the tissues by the incoming blood. In contrast, the extravascular circulation of fluid caused by net filtration and absorption is only about 2 per cent of the plasma flow as indicated in figure 5.2. For this reason the rates of exchange of small molecules between blood and tissues are but little affected by simultaneous net fluid movement. For example, *p*-aminohippurate and related substances diffuse rapidly out of the peritubular capillaries in the direction opposite to net fluid flow (peritubular capillary reabsorption). The rates of clearance of Na²⁴ or I¹³¹ from skin are not appreciably affected by concurrent edema formation (164).

The permeability of biological membranes is usually expressed in terms of flux rate per unit concentration difference divided by the area, A_m , of the entire membrane surface (specific permeability coefficient)

$$P_s = \frac{\dot{n}}{\Delta c} \div A_m = \frac{D_s A_s}{A_m \Delta x} \quad (9.4)$$

Values of P_s for muscle capillaries are listed in table 9.1. Information of the type summarized in table 9.1 is not yet available from capillaries in regions other than muscle, with the possible exception of renal glomerular capillaries (section 10). Nevertheless, there are many indications that permeability properties of capillaries may differ greatly in different organs. Studies of the rates at which labeled proteins or dextran fractions appear in lymph from different regions suggest that porosity of capillaries in visceral organs may be considerably greater than in capillaries

TABLE 9.1. *Permeability of Mammalian Muscle Capillaries to Lipid Insoluble Molecules*

| Substance | Mol Wt | $D_{37^\circ C}$ $\text{cm}^2 \text{sec}^{-1} \times 10^5$ | Approx. Mol Radius, $a \text{ cm} \times 10^8$ | $A_s/\Delta x$ Restricted Pore Area \div Path Length,* $\text{cm} \times 10^5$ in 100 g Muscle | Specific Permeability† $P = \frac{\dot{n}}{\Delta c} \div A_m$ $\text{cm sec}^{-1} \times 10^5$ |
|------------------|--------|---------------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| H ₂ O | 18 | 3.4 | 1.5 | .55 | 28 |
| NaCl | 58 | 2.0 | 2.3 | .51 | 15 |
| Urea | 60 | 1.95 | 2.6 | .49 | 14 |
| Glucose | 180 | 0.90 | 3.7 | .44 | 6 |
| Sucrose | 342 | 0.70 | 4.8 | .39 | 4 |
| Raffinose | 504 | 0.64 | 5.7 | .34 | 3 |
| Inulin | 5,500 | 0.21-.26 | 12-15 | .10-.14 | 0.3 |
| Myoglobin | 17,000 | 0.17 | 19 | .03 | 0.1 |
| Serum albumin | 67,000 | 0.085 | 36 | .0007 .00065‡ | 0.001 |

* From smooth curves of figure 9.2. † Mols/sec/cm² membrane per mol/ml concentration difference. The total membrane surface in 100 g muscle, A_m , is assumed to be 7000 cm² (281). ‡ Calculated from over all bodily arterial disappearance curves (equation 8.1).

of muscle (126, 232). Anatomical studies of visceral capillaries also suggest a relatively high degree of porosity (13). Exchange rates of lipid-insoluble molecules between central nervous system tissue and blood are far lower than in peripheral tissues (68, 185, 357) although the anatomical site of the "blood-brain barrier" has not been localized with certainty to the capillary walls. Exchanges between blood and cerebrospinal fluid are complicated by absorption in bulk through large channels in the arachnoid villi and by specific active secretory mechanisms involving the choroid plexuses and ependymal linings of the ventricular system (279).

In spite of these regional differences in capillary permeability, it may be said that over-all bodily capillary permeability, determined from arterial disappearance rates of large molecules, does not differ greatly from that of isolated muscle. For example, the average plasma clearance ($\dot{n}/\Delta c$) of a dextran fraction of known free diffusion coefficient ($D = 0.10 \times 10^{-5} \text{ cm}^2 \text{sec}^{-1}$, $a = 32 \text{ Å}$) was found by Grotte (126) to be about .6 ml per min per kg dog or $10^{-3} \text{ ml per sec per 100 g tissue}$. From equation 7.6,

$$\frac{A_s}{\Delta x} = \frac{\dot{n}}{\Delta c} \div D = 10^{-3} \div .1 \times 10^{-5} = .01 \times 10^5 \text{ cm}$$

Application of the theory of restricted diffusion (equation 7.9) for average porosities of 40, 45, and 50 Å leads to true pore areas per unit path length of 1.4, 0.5, and $0.3 \times 10^{-5} \text{ cm per 100 g tissue}$, respectively.

These values, pertaining to over-all bodily permeability, may be compared with the value of $0.6 \times 10^5 \text{ cm per 100 g tissue}$ determined by the method of osmotic transient in isolated muscle (Fig. 9.2). The close correspondence between permeability to serum albumin computed from over-all arterial disappearance curves on the one hand and restricted diffusion through the capillaries of muscle on the other has already been noted (table 9.1). Similarly, the over-all bodily filtration coefficient is not greatly different from that determined in intact extremities or isolated perfused muscle (section 6). This correspondence between over-all capillary permeability and capillary permeability determined in isolated muscle is not too surprising since muscle accounts for some 65 per cent of total body weight exclusive of skeleton and fat which do not participate to a large extent in the capillary exchange.

10. MOLECULAR SIEVING OF LARGE MOLECULES: REGIONAL DIFFERENCES IN POROSITY

In artificial systems it is possible to apply high pressure differentials for rapid ultrafiltration, and under these conditions even small molecules can be "sieved" through porous membranes as illustrated in figure 7.4. In the capillary circulation, however, the transmembrane pressure differentials are necessarily small and no appreciable steady-state concentration differences of small molecules can be maintained, even at abnormally high rates of filtration. Substitution of approximate value of $A_m/\Delta x$ and r in equation 7.15 suggests that appreciable molecular sieving should be detectable with molecules of radius 10 to 15 Å at high rates of filtration caused by venous occlusion. This prediction has been verified in perfused hind limbs for the case of inulin ($a = 12-15 \text{ Å}$) during net filtration at the rate of 0.2 ml per min per 100 g tissue. Under these conditions the steady-state concentration of inulin in capillary filtrate was found to be 70 per cent of that in plasma (281); the theoretical value calculated from equation 7.15 is 77 per cent. In the case of still larger molecules, including the plasma proteins, the restriction to diffusion becomes sufficiently great to allow a high degree of molecular sieving, even at normal filtration rates.

Grotte (126) has carried out a detailed study of molecular sieving in relation to steady-state concentrations of large molecules in leg lymph, liver lymph, and cervical lymph. Grotte worked with dextran polymers of known free diffusion coefficient and mo-

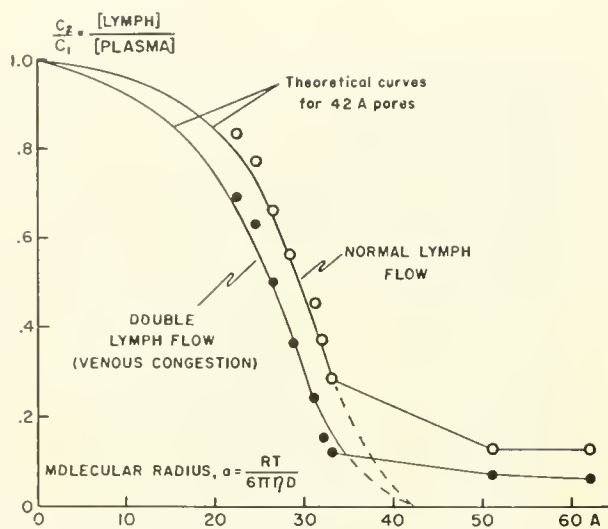


FIG. 10.1. Molecular sieving of dextrans in leg lymph obtained from dogs. The results are in accord with the theory of molecular sieving (equation 7.15) through pores of radius 42 Å and for molecules up to 32 Å in radius. Increased lymph flow induced by venous congestion produced the expected increase in sieving. The unexpected passage of dextran molecules exceeding 40 Å in radius suggests an additional "large pore" system estimated by Grotte to comprise 1/30,000 of the total population of pores. [Adapted from Grotte (126).]

molecular radius. Figure 10.1, adapted from Grotte¹ shows lymph: plasma concentration ratios as a function of molecular radius at two different lymph flows. The theoretical curves for a capillary ultrafiltrate are drawn from equation 7.15, assuming a pore radius of 42 Å, that $A_w/\Delta x$ was constant and that capillary filtration rate was proportional to observed lymph flow. The agreement between theoretical and observed concentration ratios is surprisingly good for molecules up to about 32 Å in radius. However, the observed lymph concentrations of dextran molecules ranging in size from 50 to 90 Å cannot be explained on the basis of molecular sieving through pores of radius 42 Å. In order to explain capillary permeabil-

ity to these large molecules Grotte postulated the existence of large capillary leaks, corresponding to pores of radius 200 to 350 Å but comprising only 1 part in 30,000 of the total population of pores as computed by equation 7.16. In cervical lymph and liver lymph the molecular sieving curve was shifted to the right and the relative number of calculated capillary leaks was increased to 1 in 20,000 and 1 in 340, respectively.

Concerning the locations of these leaks or large pores along the length of the minute vessels very little is known. There is some evidence, however, that they may be more frequent in the walls of venous capillaries and venules than in the walls of true capillaries. In recent studies (Landis, unpublished) solutions of T-1824 in Ringer's solution, with and without protein, have been perfused by microinjection through single vessels or through portions of peripheral networks in the frog's mesentery. Motion pictures (25–40 frames per sec) reveal sites at which the dye solutions pass rapidly through the vessel wall during the first few seconds of perfusion (fig. 10.2). In true capillaries the loci of such early, spotty passage of dye are few in number; the extravascular spots of dye are small in size and distinct in outline. In venous capillaries and venules the loci of passage are more numerous; the extravascular spots of dye tend to be larger and, particularly around venules, often coalescent. It seems likely, therefore, that while the small pore system is uniformly distributed throughout the capillary network, the leak or large pore system is more prominent in the venous capillaries and venules. A differential distribution of this type helps explain earlier work (reviewed in detail in ref. 207) on the spotty passage of certain dyes through the walls of true capillaries (200, 262) and on the gradient of permeability to poorly diffusible dyes described by Rous and co-workers (e.g., 161, 307, 308, 337, 338).

Results similar to those obtained by Grotte (126)

FIG. 10.2. Distribution of "leaks," "large pores" or gaps in the walls of the minute vessels of frog's mesentery as indicated by cinephotomicrographs of rapid, spotty passage of T-1824 (Evans blue dye). With camera running at the rate of 25 frames per sec, the dye solution was perfused through the capillary network from a micropipette introduced into the terminal, feeding arteriole. From the film thus obtained single frames have been removed to show sites and extent of dye passage at intervals of seconds (e.g., 1", 2", 3", etc.) timed from that frame in which the dye had first filled the capillaries (labeled O). The frames labeled C show the network before dye entry; those labeled 2' and C₂ after the perfusion was ended to indicate absence of stasis and hence absence of detectable injury.

Left: perfusion of .01 M T-1824 freshly prepared in frog Ringer's solution. Top section (magnification $\times 17$) shows progression of spotty passage involving true capillaries, a venous capillary and a minute venule. Middle and lower sections show greater detail (magnification $\times 60$) at 2 sec and 12 sec, respectively. *Right:* perfusion of .01 M T-1824, and 3 g/100 mg albumin, in frog Ringer's solution. Top section (magnification $\times 35$) shows spotty passage in true capillaries and a venous capillary. Middle and lower sections show greater detail (magnification $\times 120$) at 2 sec and 12 sec, respectively. Rapid, spotty passage of perfused dye persisted despite protein binding. In general, however, protein binding made spots of passage more discrete.

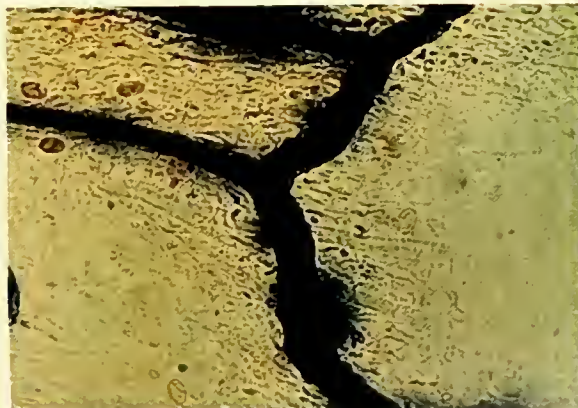
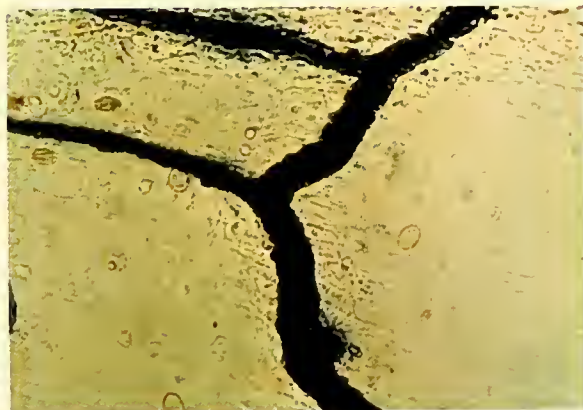
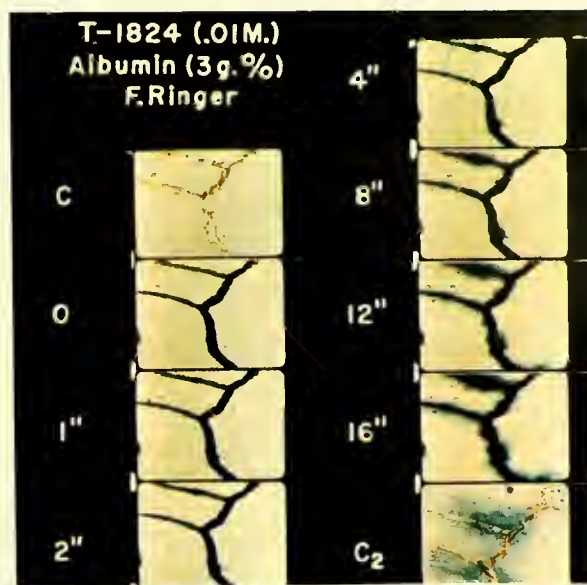
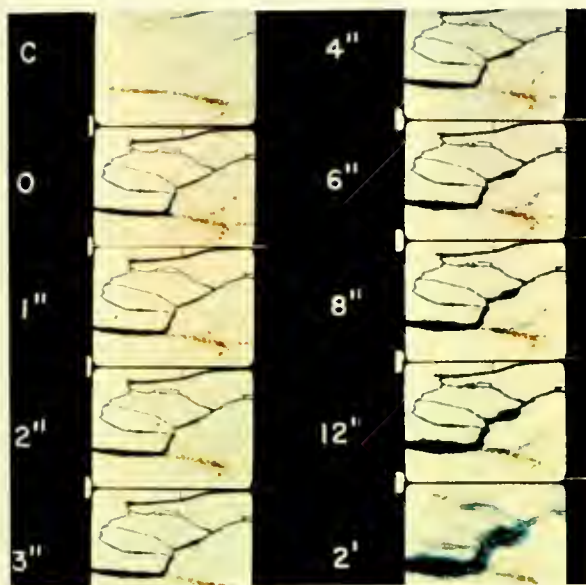


FIG. 10.2. See legend on facing page.

have been reported by Mayerson *et al.* (232) who found that dextran fractions of mean molecular weights greater than about 100,000 ($a > 60 \text{ \AA}$) appear in hepatic, intestinal, and cervical lymph in concentrations which are almost independent of molecular size. Mayerson *et al.* follow Grotte in ascribing these results to the presence of large capillary leaks but they also mention an interesting alternative possibility that very large molecules may be transported by active endothelial vesiculation (pinocytosis) as described by Palade (273) and Moore & Ruska (255). In calculating pore-size distributions Mayerson *et al.* do not take into account sieving effects nor the fact that filtration varies with the fourth power of pore radius. They assume that filtration rate through pores of given collective area will be the same, regardless of pore radius. If 5 per cent or more of the capillary pores had a radius $> 200 \text{ \AA}$, as suggested by Mayerson *et al.*, then from equation 7.16

$$\bar{r} > \sqrt[4]{0.5(200 \times 10^{-8})^4} > 95 \text{ \AA}$$

A mean pore radius of 95 \AA for hydrodynamic flow would lead to an improbably high value for the filtration coefficient. For this reason we favor Grotte's interpretation in terms of molecular sieving through pores of radius 40 to 45 \AA combined with relatively few large capillary leaks. Both interpretations are subject to the criticism that lymph is not a capillary ultrafiltrate and may well be modified by capillary reabsorption (208), particularly at low rates of lymph flow.

A more clear-cut application of the theory of molecular sieving is possible in the case of renal glomerular membranes. Figure 10.3 shows the glomerular clearances of several proteins and dextrans relative to creatinine in the dog. The apparent differences between glomerular sieving of dextran molecules and proteins of equivalent molecular radius may be spurious because the dextran fractions were not perfectly monodisperse and it is possible that the lesser degree of sieving for each nominal molecular radius represents the contribution of smaller dextran molecules. The data agree well with theoretical curves for molecular sieving through an isoporous membrane having pores 35 to 42 \AA in radius and a total pore area per unit path length for water of $1.6 \times 10^5 \text{ cm}^2 \text{ per g kidney}$ (278). Substitution of these values in equation 7.13 leads to filtration coefficients in the range $3.5 \text{ to } 5.0 \times 10^{-5} \text{ cm}^3 \text{ dyne}^{-1} \text{ sec}^{-1} \text{ per g}$ or 2.7 to 3.9 ml per min per mm Hg per 100 g kidney. These values are in excellent agreement with estimates based on hemodynamic data (339, 384). Almost identical values for renal glomerular permeability have also been derived by Lambert and his associates (194-196) from molecular sieving of hemoglobin as a function of glomerular filtration rate.

The greater permeability of renal glomerular membranes relative to peripheral capillaries is evidently due to a relatively large fractional pore area rather than to large pores. Given a path length for filtration and diffusion of $0.5 \times 10^{-4} \text{ cm}$, the glomerular pore area for passage of water would be $8 \text{ cm}^2 \text{ per g}$

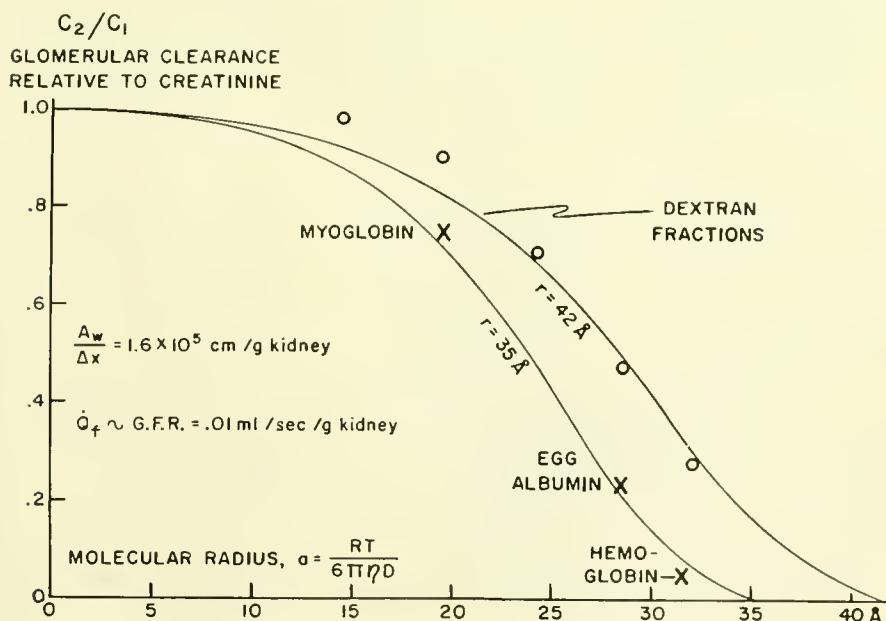


FIG. 10.3. Theoretical vs. actual molecular sieving through renal glomerular membranes of dogs. Molecular sieving of myoglobin, egg albumin, and hemoglobin calculated as in references 278 and 194. Data for dextran fractions are taken from Wallenius (366).

kidney or 5 to 10 per cent of the available glomerular surface estimated histologically by Vimtrup (360).

Recent studies of glomerular ultrastructure suggest that the anatomical basis for glomerular sieving is not in the fenestrated capillary endothelium, but rather in the epithelial cells (podocytes) covering glomerular capillaries. According to Hall (141) these cells form foot processes which approximate the endothelial basement membranes in such fashion as to form interdigitating "slit-pores" which appear to be 80 to 100 Å wide and occupy 2 to 3 per cent of the total surface.

II. CAPILLARY PERMEABILITY TO LIPID-SOLUBLE MOLECULES; RESPIRATORY GASES

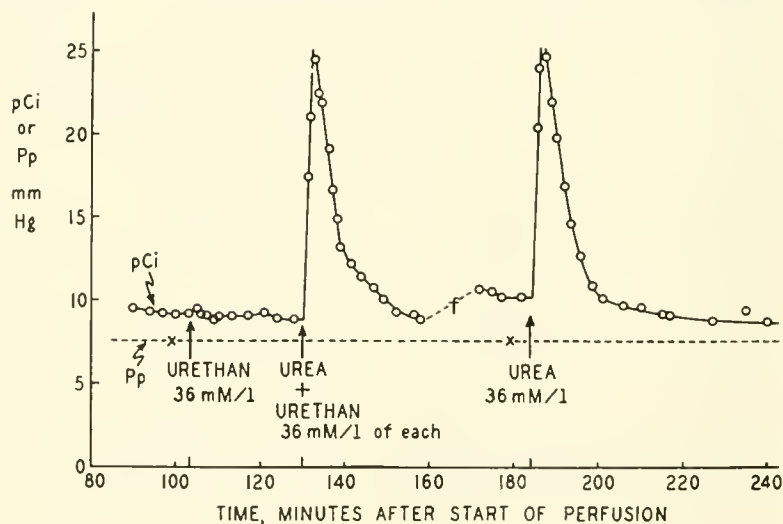
Capillary permeability to lipid-soluble molecules has been studied by Renkin (296, 297) using the perfused hind-limb preparation. Urethan (mol wt 89), paraldehyde (mol wt 132) and triacetin (mol wt 218) traversed the capillary walls so rapidly that no osmotic transients were detectable (figure 11.1). Glycerol and acetic esters of glycerol were shown to pass through capillary walls at high rates which varied in order of their oil: water partition coefficients but in order opposite to that expected on the basis of their aqueous diffusion coefficients. The temperature coefficients of capillary permeability to antipyrine and antipyrine derivatives were found to be related to the temperature coefficients of their lipid solubilities rather than to their aqueous diffusion coefficients.

These results suggest that lipid-soluble molecules can diffuse through regions in the capillary wall which are relatively impermeable to lipid-insoluble materials. The permeability characteristics of this

additional pathway are similar to those of cell membranes in general. It seems logical, therefore, to identify the diffusion pathway for lipid-soluble molecules with the plasma membranes of the capillary endothelial cells themselves, as opposed to the system of water-filled pores penetrating through or between these cells, which is capable of accounting for passage of water and lipid-insoluble molecules.

The respiratory gases have relatively large oil: water partition coefficients (212) and may therefore be expected to utilize the entire endothelial surface for the transepithelial diffusion process. Recent measurements of pulmonary diffusing capacity (306) indicate that permeability of human alveolar membranes (alveolar capillaries plus alveolar epithelium) is approximately 60 ml O₂ per min per mm Hg O₂ pressure difference. In terms of oxygen concentration difference, this value becomes $0.4 \times 10^5 \text{ cm}^3 \text{ sec}^{-1}$ (i.e., ml/sec/ml concentration difference). The capillary surface area in the lungs is approximately $4 \times 10^5 \text{ cm}^2$ (258), whence the specific permeability coefficient for oxygen is $10,000 \times 10^{-5} \text{ cm sec}^{-1}$. This value may be compared with $23 \times 10^{-5} \text{ cm sec}^{-1}$, representing the specific permeability of muscle capillaries to water (table 9.1). Presumably the greater permeability to oxygen is a result of lipid solubility, since the pulmonary capillaries resemble peripheral capillaries in being relatively impermeable to small lipid-insoluble molecules (378). In 100 g of quiescent muscle containing a capillary surface area of 5,000–10,000 cm² the steady-state flow of oxygen across the capillary walls is about 0.4 ml per min (fig. 12.2). During maximal muscular activity the oxygen requirements increase 20-fold to 30-fold and the available capillary surface may increase 2-fold to 4-fold.

FIG. 11.1. Osmotic transients produced by urethan and urea in an isolated perfused cat hind limb. pCi = isogravimetric capillary pressure. P_p = protein osmotic pressure in perfusion fluid. 36 mM/liter of urea produced a large osmotic transient owing to restricted diffusion of urea through the capillary walls. Urethan, despite its larger molecular size, failed to produce a detectable osmotic effect. The results are attributed to the greater lipid solubility of urethan which enables it to diffuse through the entire capillary endothelial surface. [From Renkin (296).]



If the specific permeability of muscle capillaries for oxygen were comparable with that of alveolar membranes, then transcapillary oxygen pressure differences of 0.3 to 0.6 mm Hg and 3 to 8 mm Hg would suffice to account for observed rates of tissue oxygen consumption at rest and during maximal work, respectively. For CO_2 the corresponding values are 20-fold smaller owing to its greater solubility. It therefore seems unlikely that capillary permeability is an important factor limiting the exchange rates of respiratory gases, except possibly during maximal muscular activity.

12. CAPILLARY PERMEABILITY AND BLOOD FLOW IN RELATION TO EXCHANGE OF MATERIALS BETWEEN BLOOD AND TISSUES

In previous sections evidence was reviewed showing that lipid-soluble molecules and small lipid-insoluble molecules or ions diffuse back and forth across capillary walls at rates which greatly exceed rates at which these substances are brought to or from the tissues by the blood. For such substances capillary permeability is clearly not an essential factor determining net rates of blood-tissue exchange. Other more essential factors include the distribution and rate of flow of capillary blood, the volume and permeability of extravascular distribution compartments, and rates of chemical reaction in the tissues. For molecules of intermediate size, including products of intermediary metabolism, capillary permeability may become more important but is still only one of the several factors determining over-all kinetics of the exchange process. Only in the case of relatively large molecules (e.g., inulin or larger) can capillary permeability be considered as a primary factor limiting exchange with well-perfused tissues.

Mathematical descriptions of diffusion kinetics in the capillary circulation are included in papers by Krogh (183), Hill (153, 154), Kety (173, 174), Opitz & Schneider (269), Morales & Smith (256), Schmidt (318, 319), Sangren & Sheppard (310), Renkin (300), and Blum (19). Each of these mathematical descriptions is based upon a particular model of capillary-tissue geometry and each involves simplifying assumptions concerning permeability which do not apply to all molecular species. Such models are nevertheless useful, if only to provide a definite hypothesis with which experimental results may be compared. Examples illustrating the use of such models are given below.

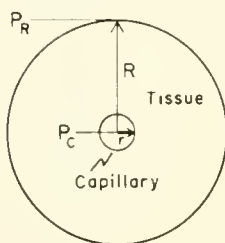
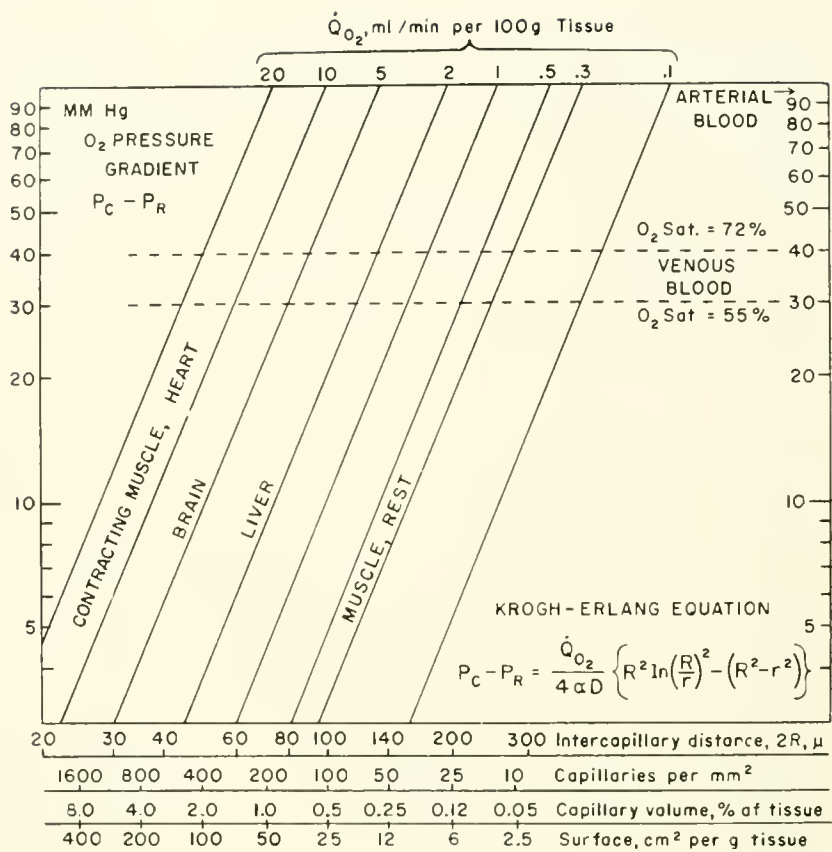
A. Blood-Tissue Transport of Oxygen

The essential role of the capillaries in the blood-tissue exchange of respiratory gases was considered by Krogh (183) in terms of spatial distribution of blood vessels relative to tissue metabolism. Krogh proposed a simple model in which each capillary of radius, r , supplied a cylinder of tissue of radius R . The intercapillary distance was therefore $2R$ and the number of capillaries per cm^2 was $(1/2R)^2$. It was assumed that rate of tissue metabolism would be uniform throughout the cylinder and that the diffusion coefficients of gases through the cylinder would be uniform and identical with values measured in dead tissues. The mathematical solution for steady-state radial diffusion under these conditions was derived for Krogh by Erlang (183) and has formed the starting point for many subsequent discussions of the blood-tissue exchange of gases [cf (174) for contemporary review].

Figure 12.1 is a graph of the Krogh-Erlang equation for capillaries of radius 4μ ; the equation is relatively insensitive to values of r and for all practical purposes the same graph applies to capillaries of radii 3 to 5μ . This model suggests that as few as 25 open capillaries per mm^2 would suffice to supply the oxygen requirements of resting muscle without exceeding the limiting diffusion pressure head set by oxygen in venous blood (i.e., a finite oxygen pressure would exist even in the outermost region of the diffusion cylinder surrounding each capillary). The corresponding figure for maximal muscular activity is 500 capillaries per mm^2 . Brain and liver would require 200 and 100 capillaries per mm^2 , respectively. Estimates of capillary density usually exceed these values by a wide margin and suggest that the oxygen pressure head required to supply the diffusion cylinder around each capillary is far less than that available in capillary blood, even at maximal rates of tissue metabolism.

Capillary counts on injected muscles from anesthetized animals lead to estimates in the range 200 to 600 per mm^2 for resting muscle and 600 to 5000 per mm^2 for contracting muscle (84, 143, 183, 227, 272, 284, 320, 335, 353). There is considerable variation among skeletal muscle, heart (305), and abdominal wall muscle (184) representing examples of high and low density, respectively. In general, muscles from small animals have a higher capillary density than from large animals (320). In maximal vasodilatation there is often a 1:1 relation between number of capillaries and number of muscle fibers, but maximum capillary density can be increased by exposure to high altitudes or by daily physical exercise (358). Capillary counts made on fixed preparations tend to be high because of shrinkage artifact; in frozen sections the muscle fibers are larger and estimated capillary densities smaller. In the author's experience, 150–200 capillaries per mm^2 is

FIG. 12.1. Steady-state radial diffusion of oxygen (\dot{Q}_{O_2}) as a function of capillary density (*abscissa*) and radial oxygen pressure gradient from capillaries to tissue (*ordinate*). [Graph constructed from the Krogh-Erlang equation (183).]



- P_C , capillary O_2 pressure, mm Hg
 P_R , tissue O_2 pressure at R
 \dot{Q}_{O_2} , O_2 consumption, ml/sec per ml tissue
 α , O_2 solubility = 2.8×10^{-5} ml/ml \times mm Hg $^{-1}$
 D , tissue O_2 diffusion coeff. = 1.5×10^{-5} cm 2 /sec ()
 R , radius of diffusion cylinder
 r , capillary radius = 4μ

usual in frozen sections of muscles from hind limbs of anesthetized cats. Many of the higher estimates imply capillary blood volumes in the range 5 to 15 per cent of tissue volume. In most skeletal muscles the entire blood volume is less than 4 per cent of tissue volume (328, 335) and at least half of this may be accounted for by large blood vessels (243). Even taking low estimates for capillary density, however, (200/mm 2 at rest, 600/mm 2 in activity) the oxygen pressure gradient predicted by the Krogh-Erlang model would be less than 5 mm Hg at rest and less than 20 mm Hg in maximum work, leading to tissue oxygen pressures of 10 to 30 mm Hg in the outermost regions of each diffusion cylinder.

The Krogh-Erlang model provides a theoretical basis for analysis of the blood-tissue gas exchange, but several lines of evidence suggest that factors other than simple radial diffusion in a homogeneous medium may be involved. In the case of skeletal muscle, Milli-

kan (253) showed that intracellular myoglobin rapidly becomes desaturated during contraction of the soleus muscle in the cat. Since the half saturation pressure of myoglobin at physiological pH is only 3 mm Hg this implies that intracellular oxygen tension falls to extremely low values during contraction. Lactic acid increases rapidly in venous blood from contracting muscle (7, 181), also indicating that oxygen supply cannot keep up with demand at high rates of metabolism, despite normal oxygen pressures in venous blood. Mechanical reduction of blood flow to resting muscle may cause substantial reduction of steady-state oxygen consumption even when the blood vessels are dilated and when venous oxygen pressure is sufficiently high to meet the diffusion requirements estimated from the Krogh-Erlang model (275, 359) (fig. 12.2). Inter-

capillary oxygen pressures may be extremely low in brain (64) despite normal oxygen pressures in cerebral venous blood. The critical venous oxygen pressure at which brain suffers a decrease in oxygen consumption is 20 to 25 mm Hg (269); presumably, under these conditions, oxygen pressure is zero in regions most remote from the capillaries.

These observations suggest that the gradient of oxygen pressure from capillary blood to tissues is greater than predicted from the simplified model proposed by Krogh. One factor neglected by Krogh's treatment of the problem is the rate at which oxygen can be released from red cells during their brief exposure to the tissues in capillary blood. Roughton & Forster (306) and Forster (108) have recently discussed evidence that chemical reaction velocity and diffusion in the red cell account for almost one-half the total resistance to transfer of oxygen between alveolar gas and blood. The rate of dissociation of oxygen from hemoglobin is slower than its rate of combination and recent measurements by Niesel *et al.* (261) and Thews (356) indicate that the intracapillary component of oxygen diffusion may be a major factor limiting the rate at which oxygen can be supplied to adjoining tissues. This factor could be evaluated experimentally and deserves attention in future studies of the blood-tissue exchange of gases. Scholander's recent demonstration of facilitated diffusion of oxygen through thin films of hemoglobin or myoglobin (321) may also be of significance for diffusion of oxygen in muscle, especially cardiac muscle.

B. Blood-Tissue Exchange of Small, Nonmetabolized Molecules or Ions

A simple model of blood-tissue exchange has been employed by Renkin (299, 300) to describe diffusion kinetics of urea, antipyrine, sucrose, and K^{42} in perfused muscle. This model is particularly useful for illustrating the relative effects of permeability and blood flow on diffusion kinetics in uniformly perfused tissue. In its simplest form the model assumes two compartments representing total blood volume, V_1 , and extravascular distribution volume, V_2 . The compartments are separated by a barrier of virtual area A_m and permeability coefficient, P . V_1 is allowed to flow past the barrier at rate, \dot{Q} . V_2 is assumed to be homogeneous with respect to concentration of diffusing materials. The mathematical solution for this model (300) is given by

$$C = \lambda \frac{V_1 V_2}{(V_1 + V_2)} = \dot{Q} \left(1 - e^{-\frac{PA_m}{\dot{Q}}} \right) \quad (12.1)$$

where C = clearance from the blood compartment, V_1 , ml per min, and λ = slope of the exponential disappearance curve from the blood compartment, min^{-1} . In perfused preparations the rate of blood flow may be varied over a wide range by simple adjustment of perfusion pressure. Clearance, C , from the perfusion reservoir can be measured accurately. It is therefore possible to determine over-all permeability, $P \times A_m$, of barriers separating blood from the final distribution volume, provided the original assumption of uniform distribution in extravascular space is correct. For many substances this assumption will not be valid and in such cases PA_m must be considered as a virtual permeability which includes the effects of nonuniform distribution in extravascular space.

Figure 12.3 shows capillary clearances of antipyrine, K^{42} and urea as a function of blood flow in widely dilated blood vessels of mammalian muscle. The changes in blood flow were produced by change of arterial perfusion pressure and presumably reflect changes in flow velocity through a constant capillary surface as required by the model. Comparison of the results with theoretical curves drawn from equation 12.1, suggest blood-tissue permeabilities (PA_m) of about 3 and 10 ml per min per 100 g muscle for urea and K^{42} , respectively. For antipyrine the observed capillary clearances were equal to blood flow, indicating that for this (lipid-soluble) substance permeability (PA_m) was large with respect to blood flow.

Blood-tissue permeabilities estimated by equation 12.1 from measurements of blood flow and clearances are compared in table 12.1, with capillary permeability estimated from osmotic transients and the theory of restricted diffusion. In the case of sucrose the blood-tissue permeability is 30 to 60 per cent of capillary permeability. Sucrose distributes primarily in interstitial fluid and the only barriers to diffusion are capillary walls and interstitial fluid volume. From the available data (table 12.1) it appears that in muscle about one-half the total resistance to distribution is located in the capillary wall. Cotlove (46) has shown that distribution rates of NaCl, sucrose, and inulin into connective tissue spaces of extremities are limited by the long path length for diffusion along fascial planes and by retardation of diffusion in the interstitial matrix. Recent measurements by Ogston & Sherman (266) indicate that diffusion of molecules as small as glucose may be appreciably restricted in dilute gels formed by hyaluronic acid and the action of hyaluronidase in reducing resistance to flow through connective tissue has been described by Day (69).

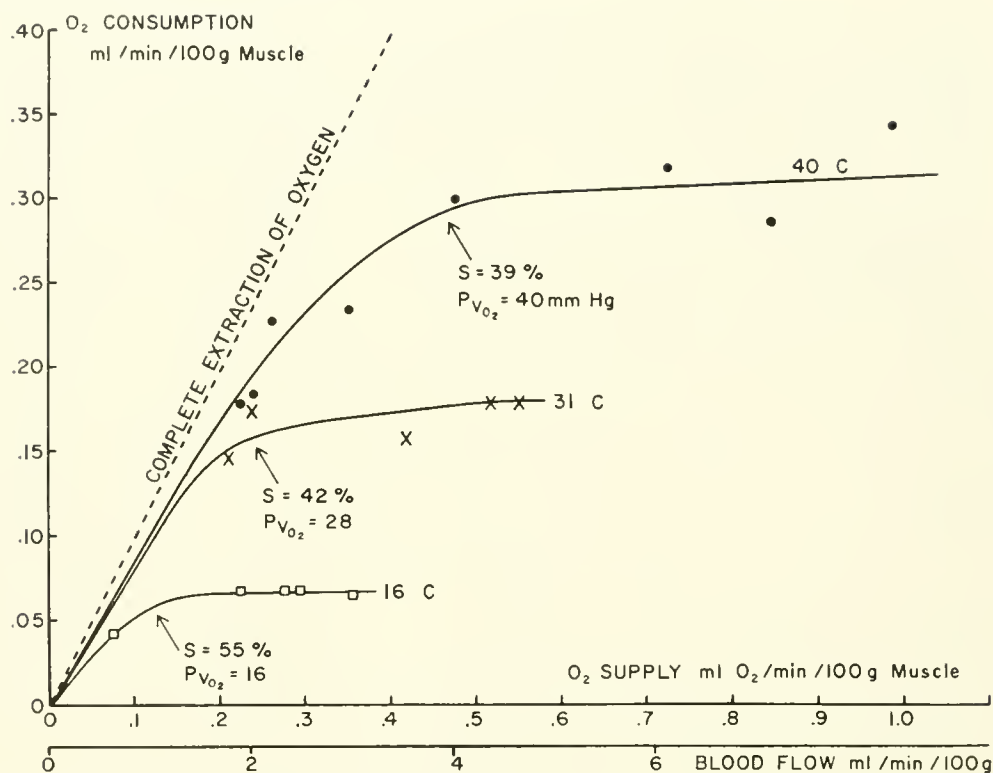


FIG. 12.2. Steady-state oxygen consumption as a function of blood flow and tissue temperature in the hind limb muscles of an anesthetized cat. Oxygen consumption was lowered when oxygen supply (blood flow) was reduced below a critical value at each temperature. Critical oxygen pressures in venous blood were 40, 28, and 16 mm Hg at oxygen consumptions of 0.3, 0.15, and 0.06 ml/min respectively. A capillary-tissue pressure gradient of less than 5 mm Hg would suffice to supply these rates of oxygen utilization by simple radial diffusion in tissue containing 100 perfused capillaries per mm: (fig. 12.1). The results indicate that the gradient of oxygen pressure from capillary blood to tissue is greater than that predicted from the simplified model proposed by Krogh (183). Oxygen saturation, S , measured by oximeter and gas analysis. Oxygen pressure in venous blood, $P_{V_{O_2}}$, estimated from measured oxygen dissociation curves at each temperature. Tissue temperature adjusted by passing femoral arterial blood through a heat exchanger. Blood flow adjusted by variable arterial resistance. (From unpublished experiments by Rapela *et al.*)

Urea and K^{42} distribute in intracellular water and for these substances the chief barrier to diffusion is probably located at cell membranes in the tissues. Table 12.1 shows that blood-tissue permeabilities to these substances are far less than respective capillary permeabilities.

When blood-tissue permeability is large with respect to blood flow, equation 12.1 approaches the limit $C = Q$ and blood-tissue distribution is said to be flow limited. This is the case for lipid-soluble molecules in general (e.g., antipyrine, fig. 12.3) and provides the theoretical basis for estimating regional blood flow from blood or tissue clearances of these substances (173). Johnson *et al.* (168) have shown that distribution of labeled water is blood flow limited in cardiac and skeletal muscle and Sapirstein (311) has used the

blood clearances of Rb^{86} or K^{42} as a measure of relative regional blood flow. The clearances of labeled Na or I from blood or interstitial space have also been used for this purpose (72, 165, 172, 290, 362) but in view of the interstitial component of blood-tissue permeability this may not be justified. Several investigators have measured fractional extractions (C/Q) of test materials during single passage through vascular beds of extremities (40, 111), head (40), liver (40), heart (44) and lungs (39). Equation 12.1 suggests that the values so obtained reflect the exponential ratios of blood-tissue permeability to blood flow under the conditions of vascular tone prevailing at the time of measurement.

For large lipid molecules the chief barrier to tissue distribution is the capillary wall and in this case PA_m

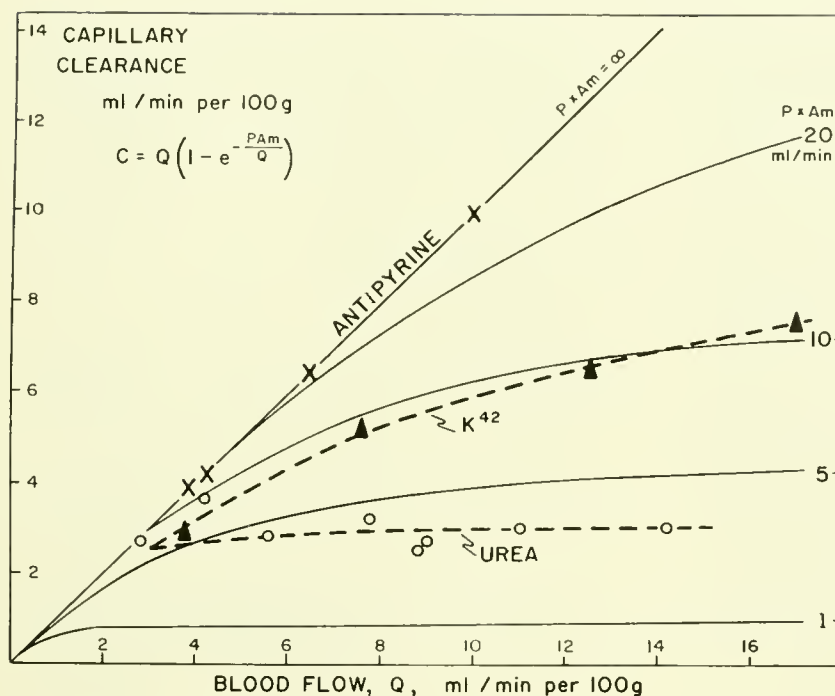


FIG. 12.3. Diffusion kinetics of antipyrine, K^{42} , and urea in vasodilated muscle. Permeability to antipyrine (lipid-soluble) is so large that its clearance is limited by rate of blood flow. The clearances of K^{42} and urea are limited, in part, by permeability of cell membranes in extravascular distribution volume. Less than 10% of the diffusion barrier to urea is contributed by the capillary wall (table 12.1). [Adapted from Renkin (299, 300).]

TABLE 12.1. Comparison of Blood-Tissue Permeability with Capillary Permeability

| Substance | Permeability, ml/min/100 g Muscle | |
|-----------|-----------------------------------|----------------------------------------------|
| | Blood-tissue PA_m^* | Capillary walls $D_s A_s / \Delta x^\dagger$ |
| Sucrose | 5-11 | 18 |
| Urea | 4 ± 2 | 54 |
| K^{42} | 7 ± 3 | 90 |

* From equation 12.1 † From table 9.1.

$= D_s A_s / \Delta x$. For these substances PA_m is small compared to normal rates of blood flow and equation 12.1 reduces to equation 8.1 describing arterial disappearance curves of large molecules.

C. Nonuniform Distribution of Blood Flow in Relation to Blood-Tissue Exchange

The model discussed in the previous paragraphs was designed to simulate effects of changes in flow velocity through a constant number of open capillaries and the results illustrated in figure 12.1 refer to widely dilated blood vessels. At any given over-all blood flow, the clearance of test molecules may be very much smaller during vasoconstriction (299, 300). In supine, anesthetized dogs the fractional extraction of antipyrine or D_2O from the circulation to extremities may be only 0.6 to 0.8 (40) in contrast to values close to unity

in perfused, vasodilated muscle (168) or the intact human forearm (111). The fraction of total blood flow passing through true (nutrient) capillaries is subject to wide variation according to metabolic demands of the tissue or to hemodynamic demands of the organism as a whole. In some tissues, such as skin, liver, or intestine, the nonnutrient fraction of total blood flow may pass through arteriovenous anastomoses of potentially large caliber; in other tissues, such as mesentery or muscle, effective physiological shunts are formed by arteriovenous capillaries (388). Nonuniform distribution of blood flow within single organs may also occur between regions of different function and metabolic rate, examples being medulla and cortex of the kidney or gray and white matter of the central nervous system.

It is obvious that nonuniform alterations of blood flow in the microcirculation will change the relations between total blood flow and blood-tissue exchange rates; conversely, it may be anticipated that quantitative studies of effective tissue perfusion will depend heavily upon information obtained from exchange rates. At the present time, available information is mostly qualitative and derives in large part from observations on muscle.

A striking example of nonuniform distribution of blood flow in skeletal muscle can be observed following electrical or reflex stimulation of sympathetic vasoconstrictor nerves. Closure of precapillary sphincters,

innervated by the sympathetic vasoconstrictor system, can stop nutrient blood flow through large areas of capillary bed, leaving blood to flow through arteriovenous thoroughfare channels or other regions of low metabolic rate. Under these conditions, total blood flow is reduced but oxygen saturation of venous blood approaches that of arterial blood (26, 274, 294) and respiratory gas exchange may be reduced to one-half or less of its normal value. In diving mammals, drastic vasoconstriction of this type greatly reduces tissue gas exchange for periods of one-half hour or more (322, 323). This is in contrast to uniform reduction of total blood flow caused by decrease in arterial pressure or infusion of vasoconstrictor drugs (274); under these conditions, oxygen extraction is increased and oxygen utilization remains relatively constant over a wide range of blood flow (fig. 12.2).

Recent investigations of the rates at which labeled ions are removed from interstitial space in muscle also suggest that vasomotor nerves control the distribution of blood between nutrient and nonnutrient circulations (165). There is general correspondence between clearance of Na^{24} or I^{131} and over-all blood flow when flow is altered by pressure, reactive hyperemia, or

exercise (72, 165, 172, 290, 362). However, activation of the vasomotor system to muscle or skin generally results in large changes of flow without corresponding changes of clearance. Hyman *et al.* (165) have shown that I^{131} clearance may actually decrease during large increases of flow caused by activation of the sympathetic vasodilator system. They suggest that vasodilator nerves act primarily to increase flow through arteriovenous thoroughfare channels.

Studies of this type are only beginning and they point to new directions for research on the peripheral circulation. The principal function of the circulation is to provide for exchange of materials between blood and tissues and it seems logical to study this function directly in terms of exchange rates. Such studies will only be meaningful, however, if the limitations imposed by over-all permeability are considered in relation to tissue perfusion. In the present article we have provided a quantitative background for assessing the role played by capillary permeability in the distribution process, indicating only briefly the contributions of interstitial diffusion, cellular permeability, or chemical reaction velocity.

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The physiologic importance of lymph¹

H. S. MAYERSON

*Department of Physiology, Tulane University
School of Medicine, New Orleans, Louisiana*

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FROM A PHYSIOLOGIC point of view, the lymphatic system is primarily a drainage system. Its need arose phylogenetically with the development of a high pressure circulation. The latter development, designed to insure an adequate supply of oxygen to

tissues, created a situation favoring transudation of fluid and other substances from the capillaries. An increase in plasma protein served to counteract partially this leakage, since the plasma proteins exerted an osmotic pressure. There still remained, however, the problem of clearing the tissue spaces of substances which had leaked out of blood capillaries or which were not absorbed into the blood stream. In this sense, the lymphatic system must be regarded as a homeostatic mechanism, important in the maintenance of the constancy of the *milieu interieur*. It is this point of view that will be emphasized in the present discussion. The role of the lymphatic system in the transport of materials from the liver and intestines to the blood stream will also be considered. No attempt will be made to cover all that has been done regarding lymph and lymphatics nor will the extensive literature on lymph nodes and lymphoid tissues be discussed. Various aspects of the general subject have been treated in depth during the last several decades in reviews and monographs (45, 58-60, 62, 66, 88, 135-137, 185, 189, 215, 223, 227, 234) and the reader is referred to these sources for basic material not included in the present review. Two recent monographs will be found most helpful (189, 234). The latter source will interest those concerned with clinical implications of disturbed lymphatic function. It also includes results of work in Hungarian and Russian laboratories not readily available in the English literature.

METHODS OF STUDY

Although lymphatics presumably had been seen by members of the Alexandrian school (Herophilos,

¹ The work described as emanating from this laboratory was supported by grants from the Research and Development Command, U. S. Army, the American Heart Association, and the U. S. Public Health Service.

300 B.C.; Erasistratus, 310–250 B.C.) the documented study of lymphatics dates from 1622, when Asellius (3) demonstrated “lacteals” in the mesentery of a well-fed dog and at a later date had the opportunity of observing these channels in a criminal who had been executed following a large meal. Jean Pecquet (169) in 1651 described the cisterna chyli and the thoracic duct. The term “lymphatics” was first used by Thomas Bartholin (12, 13) and he and Rudbeck (186) are usually considered to be the co-discoverers of the lymphatic system.² In 1692 Nuck (160) introduced the use of mercury for injection of lymphatic vessels, a method which was used extensively by many investigators during the eighteenth century to describe the location and distribution of the main lymphatic vessels. Of particular importance was the work of Hewson (99), a pupil of William Hunter, who made extensive dissections of the lymphatic system and noted that lymph glands were absent in fishes (also in the turtle), few in number in birds, and well developed only in mammals. He also noted the presence of lymphocytes in lymph and thought they came from lymph glands to enter blood via the lymph channels. Hunter himself speculated that “the lymphatic vessels are the absorbing vessels, all over the body” (101).

Anatomical studies during the nineteenth century further delineated the distribution and characteristics of the lymphatic supply of various organs (194), but it remained for Ludwig (129) and Heidenhain (96) to provide the stimulus for studies of function. Ludwig developed techniques for the collection of lymph by cannulating lymph vessels in different parts of the body. He contended that lymph was a filtrate derived from blood, a point of view contested by Heidenhain who maintained that it was actively secreted by the lymphatic epithelium. This classic controversy was finally settled by the extensive work of Starling during the first part of this century (203), who demonstrated the relationships between hydrostatic and osmotic pressures in the exchange of substances between plasma and lymph, concepts still fundamental and generally applicable. These relationships have been discussed in Chapter 29.

The study of lymph and lymphatics has lagged behind that of other parts of the circulation because of inherent difficulties in identification and dissection of the lymphatics and their cannulation. Since

lymph is virtually colorless, it does not help in the visualization of these small vessels. Even the identification and dissection of the largest trunk, the thoracic duct, is a formidable challenge to the uninitiated investigator unless its visualization is aided by previous injection of dyes or feeding of fats. Once identified and dissected, cannulation of a lymphatic still presents a problem because of the ease with which the thin vessel can be torn. This may explain the temptation for investigators to forsake the actual collection of lymph for the much less frustrating study of the effects of ligation of the vessels. Rudbeck expressed these difficulties very well in 1653 when he said:

“Of the many structures difficult to find in anatomical dissections, these vessels, I must confess, are by no means the least. For usually they will not tolerate the finest blunt probe, a sharp knife, a suction tube, or any other instrument whatever. And even though abundantly present, they are often obscured by fat, or are overlooked if not at the moment filled with fluid. When seen they may disappear if not ligated. Thus in elusiveness they rival the lacteals and must be handled with utmost care.”

Several recent developments have, however, made the lives of the lymphatic investigators less trying and their labors more rewarding. Availability of nontoxic and radiopaque dyes has facilitated tracing of lymphatic pathways and stimulated a new interest in this aspect, particularly in surgery (20, 52, 112). To the physiologist, the greatest boons have been the availability of polyethylene tubing and isotopes. The range of sizes and flexibility of polyethylene tubing and relative freedom from clotting in this tubing have made cannulation easier and have made chronic experiments possible not only in unanesthetized experimental animals but in man (16, 31, 54, 125, 177, 201, 208). Small vessels entered with glass cannulae only with the greatest difficulty can now be studied (198, 199). The use of isotopes has facilitated the study of lymphatic uptake from subcutaneous tissues (100, 209). It has also made possible more quantitative studies on the exchange of substances between plasma and lymph. These gains will be apparent in the discussions to follow.

DEVELOPMENT AND STRUCTURE OF LYMPHATIC VESSELS

It is now generally agreed that lymphatic vessels are derived from veins. To quote Sabin (190) “Lym-

² There is an interesting biographical note by G. Liljestrand and a translation of Rudbeck's “*Nova exercitatio anatomica*” by A. E. Nielsen in the *Bulletin of the History of Medicine* 11: 304–339, 1942.

phatics are modified veins. They are vessels lined by an endothelium which is derived from the veins. They invade the body as do blood vessels and grow into certain constant areas; their invasion of the body is, however, not complete for there are certain structures which never receive them. The lymphatic capillaries have the same relation to tissue spaces as have blood capillaries. None of the cavities of the mesoderm, such as the peritoneal cavity, the various bursae and serous capillaries, forms any part of the lymphatic system. The lymphatic endothelium once formed is specific. Like blood vessels the lymphatics are for the most part closed vessels."

The lymphatic capillaries may be considered as endothelial tubes resembling blood capillaries but thinner. The medium-size vessels (100–200 μ) have muscle fibers, whereas the larger lymphatics are composed of an endothelial layer covered by a diffuse connective tissue sheath in which elastic and muscular elements are irregularly scattered. Amyelinated nerves can be traced to the muscle fibers. Valves develop during intra-uterine life in the large vessels and are usually unicuspid or bicuspid. These structures determine the direction of flow toward sites of emptying into the blood stream.

LYMPH VS. TISSUE FLUID

It is now generally accepted, primarily from the work of Sabin (191) and MacCallum (132), that the lymphatics form a closed system. "Lymph," therefore, is not synonymous with "tissue fluid," but is the fluid found in lymphatics. This is more than a semantic distinction because, as will be apparent later, the composition of lymph is more particularly determined by the permeability of blood capillaries in a definite area and the consequent pericapillary filtrate than it is by the metabolism of tissue cells. In this sense, lymph is pericapillary filtrate which has mixed with tissue fluid and has entered the closed lymphatic system.

Clark & Clark (43) showed that lymphatic capillaries are sometimes closely associated with small blood vessels, with virtually nothing between the two membranes, while in other cases they bear no relationship to such vessels. In any region, the fluid that enters the lymphatic system to become lymph may be that which is adjacent to the arterial end or to the venular end of a blood capillary, or it may be fluid that is relatively distant from a blood capillary. McMaster (137) studied the relative pressures within

the cutaneous lymphatic capillaries and the surrounding tissues in the mouse's ear. He reported that the mean lymphatic pressure was 1.2 cm water and the interstitial pressure 1.9 cm water. There was always a gradient of pressure from the interstitial tissue to the lumen of the lymphatic even in conditions of increased lymphatic pressure. Presumably, whenever increased amounts of fluid are present in the interstitial tissues, the lymphatic vessels are kept open by swelling of connective tissues and increase in the tension of the fibers attached to the lymphatic capillaries (42, 43, 137, 175). Many more data are needed in other tissues and species to establish firmly the fact that a gradient of pressure is always present between interstitial tissues and the lymphatics, and is an important factor in the formation of lymph. Particularly disturbing in this connection is the recent report of Guyton *et al.* (93) suggesting the existence of negative pressures in interstitial spaces.

The close anatomical relationship between the lymphatic and venous systems has raised the question as to the relationship of lymphatic and venous pressures. Little definitive information is available, however, in this area, due primarily to the difficulties in measurement of lymphatic pressure. Many of the pressures that have been recorded are end pressures (234) and not particularly representative of the actual pressures under normal conditions of flow. Thus, Lee (124) found the average end thoracic duct pressure in dogs to be 15 cm H₂O, whereas Rouviere & Valette (185) found side pressure at the entrance to the subclavian vein to be 6.4 cm H₂O. They also found the pressure in the internal jugular vein of the same animal to be 2.4 cm H₂O, thus demonstrating the existence of a gradient capable of promoting emptying of lymph from the thoracic duct to the jugular vein. Webb & Starzl (222) found side pressures of 3.5 to 5.5 cm H₂O in the thoracic duct just above the diaphragm in anesthetized dogs. At this point, arterial pulsations affected the lymph pressure, the difference between the pressures during systole and diastole being 2 to 3 cm H₂O. Although these values are lower than those of Rouviere and Valette, they still permit of a gradient toward the vein. Irisawa & Rushmer (103) recently reported on the relationship between lymphatic and venous pressure in the legs of dogs. Although previous investigators had regarded lymphatic pressure of a resting dog leg as being too low to measure, these authors, working with unanesthetized dogs, found the leg lymphatic pressures to range from 2.5 to 12.0 cm H₂O, while the range of pressures in ankle veins was from 5.5 to

15 cm H₂O. Pressure levels in veins and lymphatics were generally very similar at rest, the venous pressures being only slightly higher. It would thus seem that pressure in the lymphatic capillaries may be comparable to the pressure in the venous end of capillaries at rest. These authors found the leg lymphatic pressure to fluctuate with respiration. With increased venous pressures, lymphatic pressure rose slowly but never reached the level of venous pressure, a reflection, perhaps, of the distensibility of lymphatics (156) and collection of fluid in the tissues. Similar experiments in our laboratory (Miller, unpublished) on the anesthetized dog also showed a lack of direct correspondence between leg lymphatic and venous pressures under a variety of experimental procedures.

DISTRIBUTION OF LYMPHATIC VESSELS

Although lymphatic capillaries spread into a tissue after the blood vessels, the density of the lymphatic plexus does not always run parallel with the richness of the blood supply. Furthermore, capillary plexuses vary tremendously in richness in different organs and tissues. For example, they are abundant in the dermis, the conjunctiva, the periosteum of bone, and in the mucosa and submucosa of the alimentary, respiratory, and genitourinary tracts, but are presumably absent in cartilage, bone marrow, the central nervous system, epithelium, and fetal part of the placenta (62). Voluntary muscle contains lymphatics only in fascial planes. It is generally believed that lymphatic capillaries do not actually reach the pulmonary alveoli, but that their distribution ceases at the beginning of the respiratory portion of the ultimate lung structure, the atrium leading into the alveolus. Likewise in the liver, the ultimate functional unit, the lobule, is not supplied with lymphatic capillaries. The fluid leaving the liver sinusoids passes through capillary endothelium and, in the lobule, lies between this endothelium and the liver cells. Lymphatic capillaries are found at the periphery of the lobule, and these carry the highly proteinized liver lymph to collecting trunks which join the thoracic and right lymph ducts. In the spleen, too, lymphatics are observed only in the capsule and the thickest trabeculae. Fluid which filters through the walls of the capillaries and sinuses must permeate the stroma before reaching the lymphatic vessels.

Lymphatic vessels in the kidney appear to begin blindly in two areas (181). The first of these is near Bowman's capsule, and the second is beneath the

mucosa of the papilla. Two networks of lymphatics then arise, accompanying venous and arterial blood vessels of the kidney. Those which originate in the medulla drain upward and outward toward the arcuate vessels, where they join with those beginning near Bowman's capsule draining in the opposite direction. When the junction occurs, larger trunks then drain with the arcuate vessels toward the hilum of the kidney. They may be seen around the renal artery. There do not seem to be any demonstrable lymphatic channels in the glomeruli or about the afferent and efferent arterioles.

The lymphatic drainage of the eye has only recently been clarified (165). The explanation of the almost zero concentration of proteins in the anterior chamber has long been a major problem since no lymphatic drainage had previously been described. Papamiliades, in an anatomical study of lymphatics at the iridocorneal angle of the eye, described lymphatic pathways in the neighborhood of the canal of Schlemm (possibly connecting with the canal) adequate to allow continual removal of proteins from the anterior chamber.

General Anatomic Arrangement of the Main Trunks

The large lymphatic trunks join the subclavian or jugular veins near their junctions. On the left side, the deep cervical duct, draining the head and neck, the subclavian duct, draining the arm, and the thoracic duct, draining the abdominal viscera and lower extremities, enter the venous system in close association with one another. The left bronchomediastinal trunk, draining the left sides of the thorax, lung, and heart may join the thoracic duct in the neck or open independently into the junction of the left subclavian and internal jugular veins. Sometimes all of the trunks empty into a sinus or dilatation from which the lymph then empties into the vein; at other times, they may form a network before entering the vein or they may all enter the vein close together but independently of one another. On the right side, the right jugular trunk, draining the head and neck, the right subclavian trunk, draining the right upper extremity, and the right bronchomediastinal trunk, draining the right side of the thorax, lung, and heart and part of the convex surface of the liver, empty into the right lymphatic duct which, in turn, ends in the right subclavian vein at its angle of junction with the right internal jugular vein. As on the left side, the

three collecting ducts not infrequently enter the vein separately at the junction of the two veins.

The thoracic duct is somewhat more complex than other lymphatic vessels. It usually begins in front of the body of the second lumbar vertebra, to the right of and behind the aorta, by a dilatation of the cysterna chyli. It enters the thorax through the aortic hiatus and ascends through the posterior mediastinum between the aorta and azygos vein. Somewhere between the fourth and sixth vertebral level it inclines to the left, enters the superior mediastinum, passes behind the arch of the aorta and thoracic portion of the left subclavian artery into the neck where, after passing in front of the left common carotid artery, vagus nerve, and jugular vein, it ends, as previously noted, by emptying into the angle of junction of the left subclavian vein and left internal jugular vein. The thoracic duct is the largest lymph vessel and is composed of an endothelial layer, a distinct subendothelial layer of elastic fibers, a media of irregularly arranged but mainly circular smooth muscle cells interspersed with elastic and connective tissue fibers, which is succeeded by the adventitia containing longitudinal and transverse bundles of smooth muscle cells as well as blood vessels and nerves. It contains valves which are quite efficient. Kampmeier (106) found many more valves in the thoracic duct of early embryos than in later stages. In one human fetus, of 4.3 months, he found 42 valves between the jugular confluence and renal arteries. In older fetuses he found as few as three complete valves with numerous vestiges present. Obviously, many of the early valves never progress to the functional stage and some vanish entirely. Kampmeier suggested that the valves which did remain in postnatal life were determined by areas of direct pressure on the duct as, for example, in the area between aorta and esophagus as they cross, an area in which a bolus of food exerts pressure upon the duct.

The above general descriptions are actually subject to more exceptions than have been indicated. Studies of large numbers of animals or species soon demonstrate this variability. McClure & Silvester (134) drew attention to this variability, as far back as 1909, in their report of a study of 25 species involving 50 mammals (primates, carnivora, rodentia, ungulata, and marsupialia). In the adult cat, communication between the lymphatic system and the systemic veins may normally occur on each side of the body, within either one of two or within two typical districts. These two districts include, approximately, the angle of confluence formed by the union of the external

and internal jugular veins (common jugular angle) and the angle of confluence formed by the union of the external jugular and subclavian veins (jugulo-subclavian angle). In the adult cat, neither one of these two districts predominates as the place of communication between the lymphatics and the veins; either one of the two, or both, may serve equally in this capacity. Their studies in other mammals showed that these two districts were the predominant sites of communication between lymphatics and veins, but there was a marked variability in lymphatic arrangement, more so than in veins, not only in different species but among members of the same species. These variations are presumably due to differences in the establishment of these connections in the embryo.

One factor which has been relatively neglected in recent years has been the possible existence of direct lymphatic communications between veins at points other than the entrance of the main ducts. Silvester (200) injected 89 adult monkeys and studied their lymphatic arrangements. He made the significant observation that "Whenever the mesenteric or inguinal lymphatic nodes of a New World species were injected, the injection mass never passed from the lumbar or intestinal lymphatic trunks into the thoracic duct or into the anterior regions of the body, but passed directly into the postcava into the region of the renal veins. A more detailed examination of the vessels in this region of the body revealed the fact that the lymphatics of the digestive organs and of the posterior extremities invariably enter the venous system at the level of the renal veins." Silvester found the posterior communications between the lymphatic and the venous system to vary from two to nine in number and to open at almost any point on the renal segment of the postcava and its immediate tributaries. He examined 16 different species of Old World monkeys and found no evidence of these communications.

It would be of great interest to know if similar communications exist in the dog, rat, and man, animals most frequently used in studies of the lymphatic system. Their existence might modify interpretations based on the supposition that all lymph from the viscera and posterior extremities finds its way back to the blood stream only via the main lymphatic channels.

CONTRACTILITY OF LYMPHATICS

In lower animals, as in the frog, lymph hearts serve to actively propel lymph and distribute it to

various parts of the organism. In the mammal, there are no lymph hearts and lymph is moved along the vessel wherever and whenever the vessel is compressed, a situation analogous to that obtaining with veins and venous flow. The presence of smooth muscle fibers in the walls of at least the larger vessels, and nerve fibers running to them, raises the question as to whether lymphatic vessels have contractility or show vasomotion. Of particular interest are their responses to sympathetic and parasympathetic stimulation and to the chemical mediators, epinephrine and acetylcholine.

Spontaneous contraction of lymph vessels was described as far back as 1774 by Hewson (99), who reported briefly of having seen actively contracting lacteals in horses and dogs killed immediately after the ingestion of food. Since then, many observers have also reported spontaneous contraction of these and other lymph vessels, but there seem to be species differences (159, 160, 175, 202, 224). Definite spontaneous contractions have been observed in the peripheral lymphatic vessels of the bat, rat, and guinea pig. No spontaneous contractions have been demonstrated in the cat, dog, rabbit, and squirrel. The results on mice have been equivocal. The few casual observations in man have shown none. The rate of contraction appears to be directly proportional to the rate of formation of lymph and the contractions are apparently initiated by an increase in intraluminal pressure. They are not dependent on neural control (225). The vasomotion in these vessels seems to be similar to that seen in blood vessels and possibly related to it. Baez and his co-workers (9) observed mesenteric lymphatics during experimental hemorrhagic shock in rats and reported that the lymphatics undergo pronounced compensatory and decompensatory adjustments recalling those seen in metarterioles and precapillaries of the same region. During the period when the animal is recoverable by transfusion, the lymphatic vessels exhibit progressive enhancement of spontaneous motion and of sensitivity to topically applied epinephrine. Reversal of these features occurs upon the prolongation of drastic hypotension. Lymph vessel adjustments after sublethal drum trauma are of a compensatory type, compatible with survival, whereas following lethal trauma, the lymphatics invariably appear atonically distended and resemble those seen in irreversible shock.

Experiments with drugs and faradic and other types of stimulation have also given equivocal results, due probably to differences in experimental procedures, in species, and in a failure to distinguish be-

tween effects on rhythmicity and on caliber of the vessels. There is a suggestion that the response of different lymph vessels may not be uniform. Thus the usual response to sympathetic stimulation or epinephrine administration, in general, appears to be a constriction (175, 187-189, 202), whereas the thoracic duct is dilated by the same procedures (1). Much more careful work needs to be done in this area.

EXCHANGE OF SUBSTANCES BETWEEN PLASMA AND LYMPH

Much evidence has accumulated during the last decade regarding the exchange of substances between plasma and lymph. As discussed previously, the availability of isotopes has made possible quantitative studies of the disappearance of labeled substances from plasma and their subsequent appearance in lymph. The availability of polyethylene tubing has facilitated the collection of lymph and, with a few exceptions, it has been collected from all areas of the body and its contents more or less completely characterized. Beginnings have been made in the study of human lymph (97, 98, 125, 192) under a variety of experimental conditions. The latter studies have been concerned with thoracic duct lymph because of the greater ease of its collection, but will unquestionably be extended in the near future to the investigation of lymph from other areas.

Concepts of capillary permeability and factors which influence it are discussed in detail in Chapter 29. Two concepts have influenced contemporary thinking in the problem of interchange of substances between plasma and lymph, 1) the familiar "Starling hypothesis," and 2) the "pore" concept of capillary permeability.

Starling maintained that the direction and rate of fluid transfer was proportional to the algebraic sum of the effective hydrostatic pressure in the blood capillaries and the osmotic pressure of the plasma proteins. While the capillary membrane was freely permeable to crystalloids, it did not allow larger protein molecules to diffuse readily. The evidence in general confirmation of Starling's hypothesis has recently been reviewed by Yoffey & Courtice (234).

Although Starling conceived the capillary membrane as being only relatively impermeable to protein, there developed a point of view implied or stated in textbooks that capillaries were impermeable to protein if they were healthy and that proteins leaked only when the permeability was abnormal. As will

be discussed in detail below, there is now no question but that "normal," "healthy" capillaries leak protein (and other macromolecules) and that the protein content of lymph collected from different areas of the body is primarily an expression of the leakage of these macromolecules from the blood stream. Thus, during the course of a day, 50 per cent or more of the total circulating protein escapes from the blood stream and is returned to it via the lymphatic system.

An additional factor in the reluctance to the acceptance of the idea that lymph was primarily derived from capillary filtrate was literal adherence to the pore concept of capillary permeability. It was difficult to reconcile the appearance of proteins and other macromolecules in lymph with the size of the "pores" postulated for capillary membranes (118). It is now obvious that the pore concept as originally reviewed by Pappenheimer (166) must be modified and reconciled with the more recent work on lymph to permit of the possible operation of active processes (141).

Drinker and his colleagues elaborated on Starling's concept of capillary permeability. As a result of analysis of lymph from different areas of the body they concluded "that the capillaries practically universally leak protein; that this protein does not reenter the blood vessels unless delivered by the lymphatic system; that the filtrate from the blood capillaries to the tissue spaces contains water, salts, and sugars in concentrations found in blood, together with serum globulin, serum albumin, and fibrinogen in low concentrations, lower probably than that of tissue fluid or lymph; that water and salts are reabsorbed by blood vessels and protein enters the lymphatics together with water and salts in the concentrations existing in the tissue fluid at the moment of lymphatic entrance" (61). During the last decade, as will be discussed below, experiments particularly with isotope-labeled proteins and other macromolecules have confirmed the point of view of the Drinker group and have shown unequivocally that "healthy" capillaries leak plasma protein and other macromolecules and that these are returned to the blood stream via the lymphatics. To date, all plasma proteins have been shown to be present in lymph from all areas studied (234).

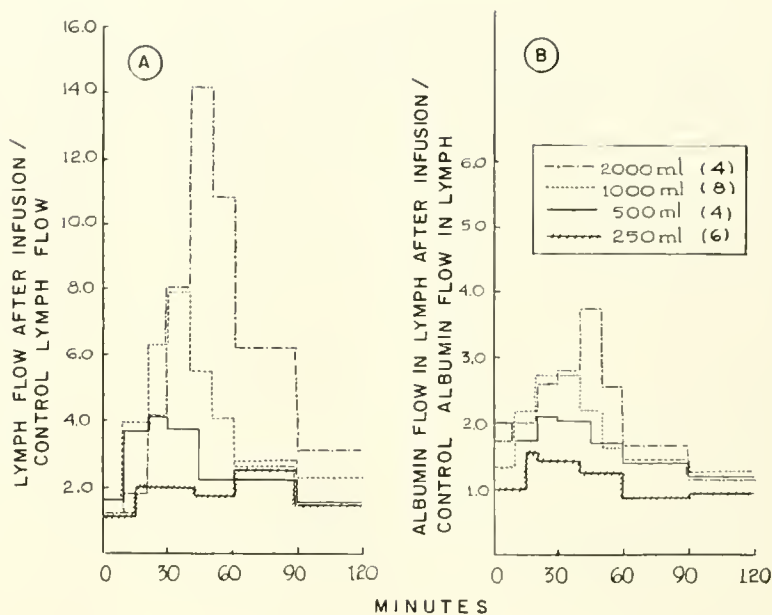
Extravascular Pool and Circulation of Protein

When a labeled protein is injected intravenously, the specific activity (ratio of concentrations of labeled

and natural protein) of lymph gradually rises (44, 116, 149) until it reaches that of plasma in 7 to 13 hours in the case of the thoracic duct (220). Samples of lymph and plasma analyzed after this time show that the specific activities in the two compartments remain equal and decline at the same slow rate. This early growth type of curve suggests that protein leaves the blood stream and mixes with the extravascular protein pool before being taken up by the lymph ducts. If lymph were a direct product of plasma, the experiments should yield a "decay" type of curve. This point of view is strengthened by experiments in which large infusions were given to dogs (116, 221). Infusions roughly equivalent to or greater than plasma volume resulted in increased flow of thoracic duct lymph and albumin leakage increased significantly (fig. 1). It was obvious that the eventual level of total circulating plasma protein was determined by a number of factors. Infusion results in the filtration of a more dilute protein solution than that filtered before the infusion, but one which has a relatively greater albumin content as well as a larger volume. This then mixes with the relatively more concentrated preinfusion interstitial fluid so that the concentration of albumin in lymph after the infusion is intermediate between that of the interstitial fluid formed before the infusion and the newly formed interstitial fluid. The eventual effect of an infusion on the total plasma protein level will thus depend upon *a*) the degree of distention of the interstitial space as a result of the infusion, since a greatly distended interstitial space may hold much of the protein which ordinarily might have gone back to the circulation via the lymphatics; *b*) the rate (and amount) of albumin leaving the capillaries; *c*) the amount of albumin present in interstitial fluid available for mixing with the plasma filtrate; and *d*) the rate of lymph flow. If the lymph does not return to the venous system or if the amount disappearing from the plasma is greater than the amount returning via lymph, plasma albumin will be decreased and remain low until the usual conditions of flow are re-established. These results with isotopically labeled albumin emphasize that we are not concerned with mobilization of cell protein, as has been suggested in the literature (4, 59), but primarily with the movement of interstitial fluid protein. Addition of new protein from any source drained by lymph coming to the thoracic duct would have been apparent by a lowering of specific activity. This was never seen.

Evidence for the existence of an extravascular albumin mass as a separate entity and in equilibrium

FIG. 1. *A*: Ratio of lymph volume flow (ml/min) after the start of the infusion to the preinfusion (control) lymph volume flow plotted against the time after the beginning of the infusion. The 250-ml infusions lasted approximately 8 min, the 500-ml infusions lasted 15 min, the 1000-ml infusions lasted 30 min, and the 2000-ml infusions lasted approximately 1 hour. Average control lymph flow for these experiments is 0.5 ml/min. *B*: Ratio of albumin flow (ml/min) after the start of the infusion to the preinfusion (control) lymph albumin flow plotted against time after the beginning of the same experiments as in *A*. Numerals to the right of the infusion volumes are the numbers of experiments which were averaged in each group. Average control albumin flow for these experiments is 8.5 mg/min.



with the intravascular mass was obtained from experiments on unanesthetized, healthy greyhounds, infused with 25 per cent albumin or bled, into which we injected I^{131} -labeled albumin and then determined the albumin specific activities (218). We showed that albumin specific activity curves can be altered by changing the ratio of intravascular to extravascular albumin masses in a manner predicted by a two-compartment system. Increase of intravascular mass (by infusion) relative to extravascular mass results in a smaller initial disappearance of albumin specific activity from the blood stream and a faster approach to equilibrium. Decrease of intravascular albumin mass relative to extravascular mass by bleeding shows that 50 per cent of albumin replacement after hemorrhage appears to be accomplished within 24 hours. Almost all this protein comes from the extravascular compartment. Rapid anabolism accounts for the replenishment of protein for the next 2 to 5 days, during and after which there is a reduced catabolism of the existing plasma albumin. Thus there are net movements from the extravascular mass into plasma when the equilibrium between intravascular and extravascular masses is disturbed.

Benson *et al.* (14) concluded that under standardized resting conditions a given tissue eliminates a nearly constant amount of protein in its lymph per unit of time and that the protein concentration in the lymph from the intestine or liver of the rat varies inversely with the volume of lymph flow. The concentrations of protein fractions in rabbit lymphs, and the rates of exchange of radioiodinated human serum

albumin between plasma and lymph which they observed, suggested that the equilibration of plasma proteins with lymph is rapid in the liver, intermediate in the intestine, and slow in skeletal muscles. These findings are consistent with our recent demonstration (see figs. 2 and 3) of differences in blood capillary permeability in different areas to macromolecules (141) and the suggestion that there are several sets of capillary pores of different sizes, large pores predominating in the liver, small pores in muscles, and both size pores in the intestinal capillaries. Alternately, the suggestion was made that cytopempsis or a similar process may be involved.

LYMPHATIC RETURN AND BLOOD VOLUME REGULATION

Lymph not only returns protein and other macromolecules from the extravascular to the vascular system but also drains fluid representing the excess of filtration over reabsorption through the capillary wall. As discussed later, the amount of lymph returned to the blood stream via the thoracic duct alone per 24 hours is roughly equivalent to the plasma volume. It is thus obvious that the return of lymph plays an essential role in the maintenance of the blood volume level. However, little definitive data is available on this point. Courtois *et al.* (50) state that in unpublished experiments on dogs anesthetized with Nembutal "the rate of escape of fluid and protein in lymph was equivalent to a daily loss of 60 per cent

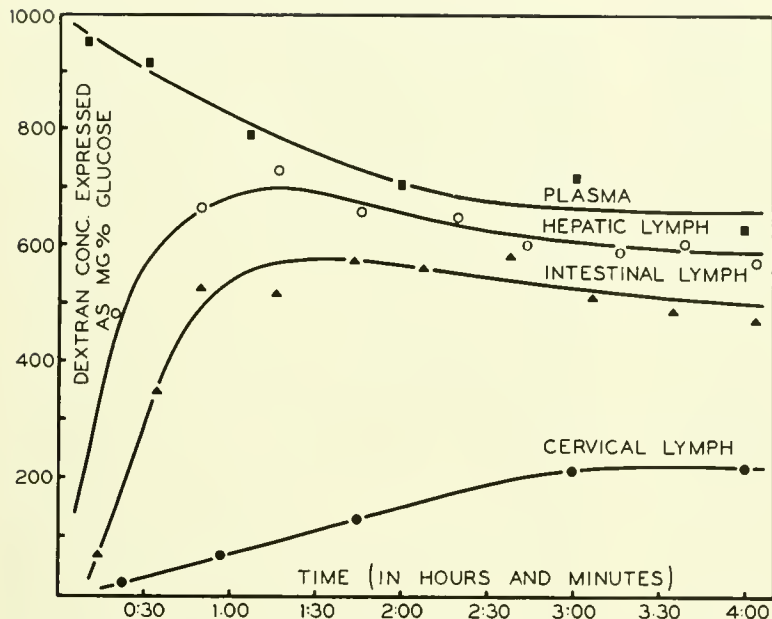


FIG. 2. Typical experiment in anesthetized dog showing disappearance of dextran of average molecular weight of 35,000 from plasma and its appearance in lymph of various areas.

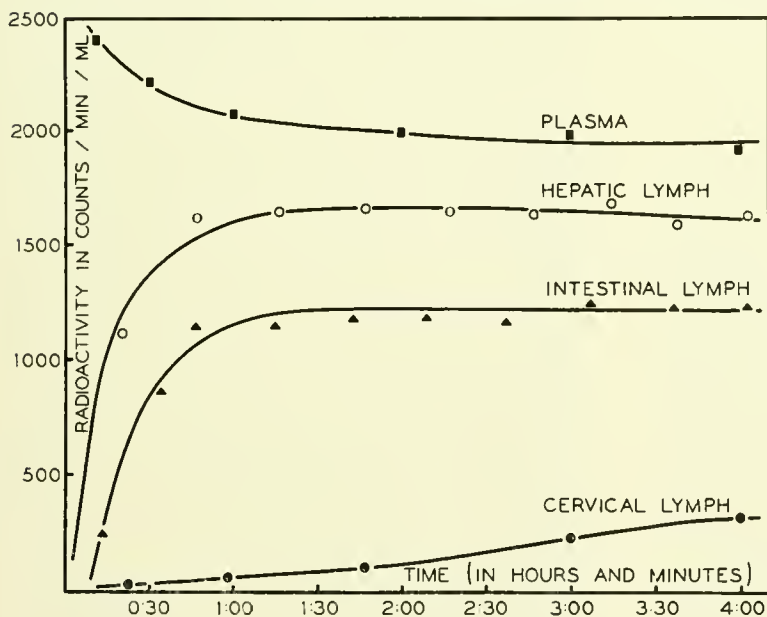


FIG. 3. Same experiment as in fig. 2 showing disappearance of radioactive albumin from plasma and its appearance in lymph of various areas.

of the plasma and 45 per cent of the circulating plasma proteins." We have confirmed these observations (Magruder, Kern, and Mayerson, unpublished). In 20 dogs, drainage of thoracic duct lymph for 8 hours resulted in an average drop of 16 per cent in plasma volume. CoTui and his colleagues (46, 196) found that when they bled dogs whose thoracic ducts were ligated there was a greater drop in the hematocrit level than in dogs bled but with intact lymphatic circulation. This hemodilution lasted at least 8 days after hemorrhage in the duct-ligated animals but

disappeared in about 48 hours in nonduct-ligated animals.

Another aspect of the problem is the well-known lymphagogue effect of infusions. As infusions are made larger, lymph flow increases proportionately so that with large infusions in dogs (2000 ml) the thoracic duct lymph flow may reach a peak value of about 14 times that of the preinfusion value (221). The displacement of fluid from the circulation supplements the diuresis through the kidneys and may be considered as a fine adjustment of the blood volume

so that not all of the fluid is irrevocably lost from the body. Large infusions also increase protein leakage but here again the protein is slowly returned to the blood stream and minimizes changes in total circulating protein and loss of its oncotic effect.

It should, perhaps, be emphasized that blood is the chief source of the water of lymph. Benson *et al.* (15) measured the content of either D₂O or Na²⁴ in intestinal lymph, portal venous blood, and femoral arterial blood of anesthetized hydrated rats after administration of the isotope into the stomach, duodenum, or peripheral or portal vein. Little, if any, water or sodium found its way into lymph after absorption from the small intestine. At least 99 per cent appeared to be carried in portal venous blood. The amount of isotope found in intestinal lymph was proportional to lymph volume whatever the route of administration. Thus, even during absorption of water or sodium ion from the small intestine, blood is the principal source of the water and sodium in lymph.

TRANSPORT FUNCTION

Lipids

There has been considerable interest, particularly during the last decade, in the transport of lipids—the physical state in which they are carried in the blood and their exchange between blood plasma and tissue cells. The availability of isotopes has facilitated the design of experiments concerned with lipid transport by lymph. It is now apparent that the lymphatic system plays an important role in lipid transport as it does in protein transport. This may be because the passage of plasma lipids through the capillary membrane depends on lipid-protein complexes rather than on the physical properties of the lipids themselves.

All the different lipid-protein associations present in the plasma have been identified in thoracic duct lymph (162), as well as in cervical and leg lymph (49). In the dog and cat, alpha-lipoprotein predominates. When rabbits are fed cholesterol, however, the plasma beta-lipoprotein may increase considerably with a much smaller rise in alpha-lipoprotein. Under these circumstances lymph contains beta-lipoprotein. The evidence suggests that beta-lipoprotein leaves the blood circulation at a slower rate than does alpha-lipoprotein. Not only do alpha- and beta-lipoproteins appear in the lymph in the postabsorptive state, but lymph from the cervical, hepatic, and leg

ducts—all draining tissues remote from the alimentary tract—also contains chylomicrons (49). As Yoffey & Courtice (234) state: “We can readily understand how the intestinal lymph always contains chylomicrons even in what we call the postabsorptive state. The presence of chylomicrons in lymph from other tissues, however, suggests that they come either from the blood stream by passing through the capillary membrane or from the fat depots. The evidence indicates that the chylomicron count in the lymph may vary with that in the blood, which suggests that these particles may pass through the capillary membrane and so appear in the lymph. For example, the hepatic and cervical lymph ducts were cannulated in a fat-fed cat and chylomicron counts made on lymph and plasma. The thoracic duct which was pouring very fatty chyle into the blood stream was then cannulated and the lymph collected. The chylomicron count in the plasma fell in the next few hours and with this fall the counts in the hepatic and cervical lymph also fell. The fatty chyle which had meantime been collected from the thoracic duct was then injected intravenously making the plasma quite milky. The chylomicron counts in the hepatic and cervical lymph subsequently rose.” Geyer *et al.* (83) attempted to assess the permeability of capillaries to serum cholesterol in humans by measuring the disappearance of cholesterol from the blood in the forearm during various degrees of venous congestion. Under these circumstances, measurable amounts of cholesterol were filtered and were related to the rate of fluid filtration and the initial level of the serum cholesterol. The results were similar to those of Landis *et al.* (119) for serum proteins. It may also be of interest to mention that the rise of plasma cholesterol occurring in the hypothyroid state does not appear to be due to any decrease in its ability to diffuse out of the plasma (79). Electron microscope studies suggest that chylomicrons can be transferred directly across cell membranes (5, 164) by the active process of pinocytosis. The probability that some active process is concerned in the transfer of macromolecules from the capillaries to lymph is discussed elsewhere (141).

When fatty chyle or artificial fat emulsions are injected into the blood stream, they leave the circulation very rapidly, but the amounts found in lymph are relatively small (140, 142, 148, 151, 233). The latter investigators injected fatty chyle collected from fat-fed cats into postabsorptive cats and determined the lipid disappearance from plasma and its appearance in hepatic, intestinal, and cervical lymph.

These calculations showed that protein left the circulation at the rate of 77, 142, and 11 mg per hour in the liver, intestine, and cervical tissues, respectively, or a total leakage of 230 mg. In another cat, 2540 mg of injected fat left the circulation within 2 hours during which time the leakage of protein was 448 mg. It is obvious that fat in chylomicron form can disappear from the blood stream much faster than protein. The chylomicron fraction of lymph appears to carry neutral fat (233).

Reinhardt *et al.* (182) injected biosynthesized P^{32} -labeled phospholipid into a peripheral vein of rats with thoracic duct fistula and reported that 9 to 20 per cent of the injected phospholipid could be recovered in the thoracic duct lymph in the succeeding 3 to 6 hours. McCandless & Zilversmit (131) obtained labeled lymph by feeding dogs with I^{131} -labeled triolein. The labeled lymph was administered to recipient dogs, and the rate of disappearance of the lymph lipids from plasma was followed. Lymph I^{131} triglycerides were found to disappear from the circulation rapidly, with an initial half-time of several minutes. Disappearance of I^{131} phospholipids was slower as determined in the same animals, 10 to 40 per cent of the injected dose remaining in the blood 1 to 2 hours after injection. These results were similar to those previously obtained by the same authors using artificially prepared fat emulsions (130).

The presence or absence of bile appears to influence the pattern of absorption and lymph transport of dietary soaps and triglycerides in the dog. Rampone & Sigurdson (179) recently reported that the absorption of triolein and sodium oleate was significantly diminished in the absence of bile. In the normal dog, 90 per cent of fed triolein and 94 per cent of fed sodium oleate were recovered from the thoracic duct as lymph lipid. In dogs with bile fistula only 8 per cent of fed triolein was recovered in lymph compared to 40 per cent of sodium oleate.

The route of absorption of steroids from the gastrointestinal tract seems to be determined largely by the chemical nature of the compounds. Methyl testosterone, 17α -methyltestosterone and cortisone- $4-C^{14}$ acetate are absorbed in the rat by way of the portal circulation (23, 24, 102). Studies in human subjects have shown that testosterone, cortisone, and cortisone acetate are also absorbed in this manner and are virtually absent from lymph (97). In contrast, absorption of cholesterol into lymph of the rat (17, 41) and dog (152) accounts for essentially all the sterol that enters these species from the diet. This is also true for man (98). Data from the different species

studied is consistent in showing that much of the cholesterol is esterified by the intestinal mucosa (25, 41, 98, 213). A number of factors appear to influence the lipid composition of lymph during cholesterol absorption (212). In rats given intragastrically emulsions containing cholesterol, oleic acid, and sodium taurocholate, addition of albumin resulted in a rapid increase in total lymph lipid which was much more marked than in those animals not receiving albumin. The amount of lymph cholesterol, however, was less for a 24-hour period. The presence of taurocholate and oleic acid in administered emulsions resulted in elevation of ester cholesterol, indicating increased absorption of endogenous cholesterol (211). Addition of cholesterol to the emulsions also resulted in further significant increase in the ester cholesterol fraction in thoracic duct lymph. In further studies (207), it was shown that small doses of fed cholesterol- $4-C^{14}$ lead to labeling of cholesterol fractions of mucosa and lymph without an increase in the level or turnover in lymph. Feeding tracer dose with oleic acid and sodium taurocholate increases the turnover rate of the pool which leads to an increased amount of labeled and unlabeled cholesterol in lymph. In fasting rats, the major fatty acids in lymph are palmitic, linoleic, and oleic acids with polyunsaturated fatty acids comprising 36 per cent of the total cholesterol fatty acids (206). After feeding oleic acid only 42.3 per cent of the total was present as oleic acid. The total cholesterol fatty acid composition of lymph is evidently determined not only by dietary fatty acid, but by the composition of the fatty acid pool in the mucosa from which fatty acids are drawn for esterification of cholesterol, a suggestion which had been made earlier by previous workers (30).

Bloom *et al.* (22) fed unanesthetized rats C^{14} -labeled stearic and myristic acids and found that nearly all the absorbed C^{14} was recovered in intestinal lymph. This finding, taken in conjunction with earlier work with labeled palmitic and pentadecanoic acids, showed that lymph is the major if not the exclusive agent for the transport of absorbed long-chain fatty acids. On the other hand, when similar experiments were carried out with labeled lauric acid and decanoic acid, recoveries of the absorbed C^{14} amounted to 15 to 55 and 5 to 19 per cent, respectively. Since it was shown that the findings were not the result of bacterial action, it would appear that the major portion of a short-chain fatty acid is transported via the blood stream from its site of absorption. Blomstrand *et al.* (21) have extended this type of study to man. They

found that linoleic acid-1-C¹⁴ incorporated in dietary triglycerides, or fed as free acid, becomes esterified with the same classes of lipids in human thoracic duct lymph as oleic and palmitic acid. Evidently, digestion and absorption of these fatty acids are comparable, as well as their transfer into intestinal mucosa and resynthesis in lymph lipids. This is in confirmation of work on animals by the same group. They also confirmed earlier findings on animals that stearic acid-1-C¹⁴ was found in a higher percentage incorporated in lymph phospholipids than was found for linoleic acid and for palmitic and oleic acids. After isolation of lymph lecithins, there was a difference in the position of the label in lecithins of lymph according to the fatty acid used. After feeding linoleic acid-1-C¹⁴, approximately 75 per cent of the label in lymph lecithins was localized in the alpha-position. With stearic acid-1-C¹⁴, however, about 80 per cent of the label was found in the beta-positions. Their evidence indicates that there is a distinct manner in which stearic acid-1-C¹⁴ and linoleic acid-1-C¹⁴ are incorporated into thoracic duct lymph lecithins, reflecting probable differences in their metabolism.

Rampone (178) recently reported experiments in which he measured phospholipids of lymph in relation to the total lipid in 16 dogs with chronic thoracic duct fistula during the postabsorptive state and following the administration of various lipid types (triolein, soya lecithin, oleic acid, etc.) in the diet. He found that phospholipid transport related linearly to total lipid transport under all conditions studied, including the postabsorptive state. The percentage of lymph lipid transported as phospholipid ranged from 3 to 18 per cent and was independent of the type of lipid fed. Depriving the animals of phospholipid precursors in the diet for as long as 90 days previously failed to alter this relationship or the total quantity of lipid transported. Since the phospholipids increased linearly with the total lipid under all conditions studied, Rampone believes it likely that the phospholipids associate with the absorbed lipid in some manner which relates to lipid transport, possibly serving in the capacity of chylomicron emulsion stabilizers during the transport phase. He points out that while the plasma may be the source of the phospholipids, the rate of filtration from plasma to lymph would be somehow dependent on the lipid concentration in lymph, since the phospholipids of lymph increased in proportion to the total lymph. Previous work by Bollman *et al.* (26) suggests that the mucosa of the small intestine may normally be

the source of phospholipids for plasma during fat absorption.

An interesting application of the study of lymph and its possible role in the pathogenesis of atherosclerosis was reported by Kellnor (111). He collected leg lymph from rabbits rendered hyperlipemic by cholesterol feeding, by the injection of the surface-active agent Triton A-20, and by the injection of alloxan. He found (as have others) that leg lymph contained protein in a concentration equal to one-third to one-half that of the blood serum. Electrophoretic analyses showed a pattern similar to that of serum. The total lipid concentration was also about one-third to one-half that of blood serum and the major lipid fractions, cholesterol and phospholipid, were present in lymph in about the same relationship. In the cholesterol-fed rabbits, the leg lymph showed a striking increase in lipids as did the serum. On the basis of his results he concluded that: "It seems likely that under normal conditions there is a constant flow of fluid containing various serum lipids and proteins across the endothelium into the walls of blood vessels; this material normally passes through the wall and is completely removed by way of vasa vasorum and lymphatics. In certain conditions, however, where there are increased amounts of lipid in the blood, or where there are excessive quantities of certain types of lipids (beta-lipoproteins of the S_f 12-20 molecules of Gofman), the removal of these particles from the wall of the vessel is incomplete and some remain behind to initiate the process of atherosclerosis. In hypertension, the increased hydrostatic pressure appears to cause an increase in the quantity of serum lipoprotein that diffuses across the vessel wall, thereby increasing the possibility for incomplete removal and hence for deposition of lipids. In those areas of the vascular tree where the removal mechanism has been altered, as for example in syphilitic aortitis or in experimentally produced trauma to the vessel wall, the free transport of lipid and other particles across the vessel wall is impeded, and in these areas the lipid is therefore more apt to precipitate and to give rise to atherosclerosis. In this theoretical formulation of the pathogenesis of atherosclerosis, the artery wall is regarded as an organ which is constantly bathed by a serum transudate containing, among other things, various serum lipoproteins, most of which pass on through, some of which doubtless are metabolized locally, and a few of which remain behind to cause mischief. Atherosclerosis, broadly considered, may thus result either from qualitative or quantitative changes in the serum lipoproteins

that filter constantly across the walls of blood vessels, or from local structural changes inherent in the vessel wall, or the result of age or disease, that serve to hamper the normal passage of these fatty substances."

Enzymes

Many enzymes are found in lymph in small concentrations (234). Their concentrations are usually higher in intestinal and liver lymph than in cervical or leg lymph, but are usually lower than in plasma and run parallel with the concentration of proteins (18, 28). It is probable that, in most instances, these substances have leaked from the blood stream and take part in the extravascular circulation via the lymphatics.

On the other hand, certain enzymes seem to be transported to the blood stream from their cells of origin via the lymph. Flock & Bollman (74) made an interesting comparison between the activity of rat intestinal lymph with respect to amylase and tributyrinase. The activities of the two enzymes in intestinal lymph are generally less than in plasma. The 24-hour secretion of amylase in lymph is greater in fed than in fasting rats, but much of the increase is due to the increase in lymph volume. External drainage of lymph for 2 days does not significantly alter the plasma amylase level. On the other hand, although the 24-hour secretion in lymph of tributyrinase is also much greater in fed than in fasting rats, it appears to represent a specific effect of ingested fat on the chemical composition of intestinal lymph. External drainage of the lymph markedly decreases the tributyrinase content of plasma. These results are similar to those previously obtained by the same authors with respect to alkaline phosphatase (72). The increase of alkaline phosphatase of intestinal lymph following the feeding of fat is abolished or greatly diminished when the bile duct is ligated or the bile drained away in a biliary fistula (73). The presence of bile thus seems to be essential for the release of alkaline phosphatase from the intestinal mucosa.

The histaminase activity of lymph has received considerable attention from Carlsten and his colleagues. They were led to these studies by their failure to demonstrate the presence of histamine in venous blood during reactive hyperemia and muscular tetanus, where histamine was alleged by some investigators to be liberated. They then turned to lymph on the grounds that lymph is closer to the tissue cells which are thought to liberate histamine, and

therefore histamine should accumulate in greater concentration in lymph than in plasma. They used dogs, anesthetized with Nembutal, and collected lymph from the thoracic duct (37). Lymph had no histamine in detectable amounts. In contrast to guinea pigs, rats, and rabbits, dogs show low plasma histamine activity. The plasma histamine concentration could be raised to very high levels by histamine infusion or by intravenous injection of histamine liberators (curare and trypsin) without the appearance of detectable amounts of histamine. Study of the histaminolytic activity of the lymph showed it to be more than 30 times as powerful as in plasma when tested *in vitro*. *In vivo*, intralymphatically administered histamine was inactivated at a very high rate. This same group has also used cats and have described a simple micromethod for estimation of the small amounts found in lymph and plasma (38, 231), and showed that the histaminolytic activity of lymph is not changed by routine procedures such as anesthesia, laparotomy, gentle handling of the viscera, or by reactive hyperemia or pregnancy (35, 232). Adrenalectomy is followed by a marked increase in histaminase content of thoracic duct lymph (but not in plasma) which reaches a maximum within 2 hours and persists approximately 24 hours (36). Infusion of an adrenocortical extract will reverse this increased activity (39). The histaminolytic activity of cervical and leg lymph is less than that of the thoracic duct and seems to originate from the kidneys and gut (34).

It has been suggested that the lymphatic transport of lipase may be concerned with the changes seen in disseminated pancreatic fat necrosis (171). So-called pancreatic and peripancreatic fat necrosis is supposedly due to the splitting of neutral fat into glycerol and free fatty acid by pancreatic lipase which has escaped from the injured pancreas. The free fatty acids are thought to combine subsequently with calcium in the tissue and tissue fluids to form insoluble calcium soaps which give rise to the opaque white areas seen in the fat depots of the abdominal cavity and elsewhere. Perry made intraperitoneal injections of a mixture of pancreatin and graphite suspension in rats and at necropsy found multiple areas of fat necrosis in the abdominal and thoracic cavities, closely associated with graphite-delineated lymph channels. The evidence of the participation of the lymphatics in this disease is quite suggestive and indicates the desirability of further investigation of the role of lymphatics in this and other diseases.

Reizenstein *et al.* (183) recently reported experi-

ments on two beagles to which they gave $\text{CO}^{58}\text{-B}_{12}$ by stomach tube and measured its absorption and distribution between thoracic duct lymph and plasma. They found only a very small amount of the total dose in lymph which they believe to have leaked from the plasma. They interpret their results as suggestive that vitamin B_{12} is absorbed directly into the blood stream as a compound with a molecular weight only slightly higher than that of pure crystalline B_{12} . If it were absorbed as the entire intrinsic-factor-molecule (mol wt $\pm 70,000$) more should have been found in the lymph, since this large molecule probably cannot easily get into the plasma.

Coagulation Principles

Lymph from all parts of the body clots, but does so less readily than plasma. The concentrations of fibrinogen and of prothrombin in lymph are always less than in plasma and vary considerably in different regions just as concentrations of other proteins vary. Mann *et al.* (139) drained intestinal lymph from rats and found that marked hypoprothrombinemia developed rapidly, usually within 24 hours. If adequate amounts of vitamin K were administered parenterally, a normal level of prothrombin was maintained, despite loss of lymph. Transfusion of twice the animal's normal volume of plasma did not maintain a normal value for prothrombin while lymph was lost. Under the conditions of their experiments, it appeared that vitamin K was absorbed practically exclusively through the lymph and very little of it was stored, whereas the turnover of prothrombin was extremely rapid.

The concentration of fibrinogen of canine thoracic duct lymph is about 50 per cent that of plasma (29, 70). Brinkhous & Walker (29) found that the mean prothrombin level, expressed as a percentage of that in the plasma, was 93.2, 51.2, and 7.6 for hepatic, thoracic duct, and leg lymph, respectively. These findings are consistent with the known differences in permeability of capillaries to macromolecules in the leg and liver. Infusion of heparin into anesthetized dogs (214) prolonged thrombin and prothrombin times of plasma immediately, but the effect was delayed in thoracic duct lymph and required larger doses for its production. The differences between plasma and lymph were more marked with cervical lymph, which again may reflect the differences in permeability between the capillaries in the areas drained by the cervical and thoracic ducts.

Langdell *et al.* (120) have extended and, in general, confirmed these observations. They also found that lymph samples are not fully active at the time of collection. On exposure to glass surfaces in the presence of anticoagulant, the clotting time becomes shorter during the first 20 to 40 min. Coagulating lymph has a high residual prothrombin even after 18 to 24 hours in glass containers. Thoracic duct lymph contains sufficient thromboplastic materials so that adequate amounts of thrombin can form to produce a fibrin clot, but it does not contain the thromboplastic materials required for complete prothrombin utilization. These authors conclude "thoracic duct lymph in this respect might be compared with platelet-poor native plasma; however, the initial phase of relatively rapid prothrombin utilization in clotting lymph is unlike the slower initial utilization reported to occur in platelet-deficient plasma systems. The nature of the thromboplastic material in lymph is not known, but it would appear that the lipid materials being transported could furnish clot-accelerating activity. Additional studies are needed to evaluate the role of the lipid materials in the coagulation of lymph. Such studies promise to furnish considerable information on the role of alimentary lipemia on blood coagulation since lymph drains directly into the venous circulation."

Iron

The demonstration of iron within leukocytes of the intestinal villi, subsequent to the oral administration of iron, led Macallum, in 1894, to suggest that leukocytes are partially responsible for the transfer of iron from the intestine (133). Since then, other investigators (81, 84) demonstrated an increase of iron within mesenteric lymphatics after oral iron administration and suggested that lymphatics are involved in iron absorption and transport. Histochemical studies indicated that phagocytes might be concerned in mediating the transfer of iron from the intestine into the lymphatics (84), but more recent evidence does not support these concepts. Thus, Moore *et al.* (147) showed that iron absorbed from the intestine of dogs passes directly into the blood stream and only a minimal amount appears within the intestinal lymphatics. Endicott *et al.* (68) showed that the iron demonstrable in intestinal lymph of dogs and guinea pigs was derived from sources other than a single test meal. They showed that in the dog iron was transported chiefly via the portal vein with

only an insignificant amount appearing in thoracic duct lymph. Similar conclusions were reached by Reizenstein *et al.* (183). Koler & Mann (115) found that the iron content of intestinal lymph of cats maintained on a normal diet was relatively constant over periods as long as 7 days. At lymph outputs of 1 ml per hour, there was an hourly output of 0.5 μ g of iron. Peterson & Mann (174), using radioiron, found that only an insignificant portion of an orally administered amount of radioiron appeared in the lymph of rats with total intestinal-lymph fistulas—less than 0.1 per cent of the total amount of radioiron administered and only 2.0 to 5.0 per cent of the total amount of iron absorbed from the gastrointestinal tract after 8 hours. Everett *et al.* (69) confirmed these results in the rat. The absorption of subcutaneous FeCl_3 occurred primarily via the blood vessels, but subcutaneous plasma-bound iron passed almost exclusively into the lymphatics. Intravenously administered iron appeared rapidly in the lymph. These observations and those of previous workers are unquestionably related to the fact that iron is normally bound to protein in plasma. Since proteins leak slowly from blood capillaries, we would expect to find small quantities of iron-protein compounds in lymph from all areas. Since the capillaries of the intestine are more permeable to protein than those of other areas, and since protein leakage is greatest in the liver, larger amounts would be present in intestinal, hepatic, and thoracic duct lymph. It is also of interest that Everett and co-workers found no evidence that leukocytes played more than a negligible role in iron absorption regardless of the method of iron administration.

Miscellaneous

Scattered reports deal with a variety of substances transported in lymph. Thus Salter (193) reported that the protein-bound iodine per gram of protein in cervical lymph was concentrated relative to the homologous serum value. Klitgaard *et al.* (113, 114) found that about 3 per cent of a subcutaneously administered dose of thyroxine- C^{14} appeared in thoracic-duct lymph in rats during an 8-hour experimental period. The level of radioactivity in lymph was lower than in plasma on a volume basis but significantly higher when calculated on the basis of protein content. Chromatographic analysis of lymph samples showed the radioactivity present to be from unaltered thyroxine. It would be interesting to know

the extent to which other protein-bound hormones are transported in lymph. We can assume that small quantities escape from the capillaries as do other macromolecules and are returned via the lymphatic system.

Dietrich & Siegel (53) recently reported an interesting study designed to determine whether nucleotides or nucleotide precursors synthesized in an organ or tissue, e.g. liver, were available to nourish other tissues and organs. The stimulus for their studies arose from observations that certain cell types cannot utilize free bases and must secure the nucleoside containing the base from an external source, apparently other cell types. They argued that if bases and other nucleotide precursors are secreted by a distant organ or cell type, these compounds may be present in both the blood and lymph which bathes the cell or organ. Blood, however, contains such a mass of living cells that it is difficult to determine whether intermediates found in the plasma are derived from the cells within the blood or from other somatic cells nourished by and yielding their products to the blood. Since the cell population in lymph is insignificant when compared with that of blood, it might be assumed that metabolites found in the lymph would reflect more closely the metabolism of the tissue through which it has passed than that of the lymphocytes. Working on rats anesthetized with Nembutal, they injected glycine-2- C^{14} and nicotinamide-7- C^{14} and found adenine, guanine, cytosine, uracil, and uric acid in measurable amounts in thoracic duct lymph. No detectable quantities of nucleosides were observed. The quantity of acid-soluble nucleotides found was equivalent to that which would be expected from the lymphocytes present in the lymph samples analyzed. Lymph collected for a 45-hour period following the injection of carbon-labeled glycine contained no significant amount of labeled purine derivatives. At the end of this period, however, liver tissue still contained appreciable quantities of labeled acid-soluble nucleotides. Lymph collected for a similar period of time after the injection of carbon-labeled nicotinamide contained very small amounts of radioactivity. While the results raised many unexplainable questions and suggested the need of further work, they did confirm previous investigations of plasma in indicating that if these compounds are essential for the proper nutrition of certain cell types, these purine derivatives are not transported from sites of synthesis, such as the liver, via the lymphatic ducts.

SIGNIFICANCE OF SOME REGIONAL LYMPHATICS

Thoracic Duct

The size, high rate of flow and accessibility for cannulation have made the thoracic duct the duct of choice in studies on lymph. A considerable amount of data has therefore accumulated during the last 125 years relative to its characteristics under a variety of conditions in many species, including man (50, 51). During the last decade, as previously indicated, the advent of polyethylene tubing made possible chronic experiments in which the cannulas could be left in place and the data collected in the unanesthetized animal and man and in a reasonably "normal" physiological situation.

The thoracic duct receives lymph from the abdominal viscera, the lower part of the trunk, and the lower extremities, and empties it into the jugular vein. The rate of flow in the thoracic duct is greater than the sum total of flow from all other ducts. Yoffey & Courtice (234) have assembled available data on the rates of flow in the dog, cat, rabbit, rat, horse, bull, cow, goat, and man. To this list may be added the data of Shrewsbury on the mouse (198). It is interesting that in spite of the many variables involved in the experimentation (anesthesia, time of feeding, duration of collection, etc.) the thoracic duct lymph flow in all species studied averages about 2 ml per kg per hour in nonruminants and somewhat more in ruminants. If we accept the average figure for plasma volume for most animals of 45 ml per kg, it is obvious that the amount of lymph returned to the blood stream via the thoracic duct per 24 hours is roughly equivalent to the plasma volume. The above calculations are in terms of the quiet, resting animal. Under conditions of activity, the return is considerably greater.

Hepatic Lymph

The contribution of the liver to thoracic duct flow appears to be variable. It may contribute from one-fourth to one-half of the flow in the dog (33) and cat (149, 150), and only about 10 per cent in rats (138). Actually, the anatomy of the hepatic lymphatic drainage is such that direct measurement of total hepatic lymph flow is difficult and the data available have been derived from indirect estimates or from experiments where usually only one large hepatic duct was cannulated. The values obtained by such direct cannulation (0.4–1.2 ml/kg/hour) suggest that liver lymph flow is higher than that of any other part of the body of the dog.

Two hilar lymphatic pathways have been described for the canine liver (184): 1) a main hilar system, draining predominantly the right lobes; and 2) an accessory hilar system, draining mainly the left lobe. Usually all of the hilar lymph seems to pass into one common efferent trunk which then discharges it into the cisterna chyli. About 80 per cent of lymph leaving the canine liver probably travels by the hilar route and the remaining 20 per cent by the hepatic venous lymph route.

Not only is liver lymph flow higher than from anywhere else in the body, but it also has the highest protein concentration, equaling from 80 to 95 per cent of plasma concentration in dogs, rats, and cats (141, 149, 157, 158, 234). Electrophoretic analyses show that protein distribution in hepatic lymph is similar to that in plasma. These data are derived from acute experiments on anesthetized animals, from animals with chronic lymph fistulae, experiments in which T-1824 or other dyes have been used to label proteins, and from isolated liver preparations.

The extraordinarily high permeability of the hepatic endothelia involved in hepatic lymph formation has been demonstrated by the use of dextran fractions of graded molecular weights (92, 141). While the results of these investigations differ in details, they are consistent in showing that high molecular weight dextrans appear in hepatic lymph in greater concentration than in lymph from other areas (fig. 4) and suggest that hepatic lymph represents a plasma filtrate formed in a region of highly permeable capillary walls. In a recent review of hepatic circulation (27) Brauer suggests: "As a working hypothesis compatible with the major part of the available data, one may accept the following: Liver lymph formation involves two sites. The first of these would appear to be the sinusoidal portion of the hepatic vascular tree where a very large area of endothelium with demonstrably large pores surrounds the blood stream, and where one would expect the formation of a large volume of lymph, differing from the blood principally in the absence (in the normal liver, at least) of erythrocytes and of the greater part of the leukocytic elements. This primary lymph for the most part moves countercurrent to the blood stream to enter the lymphatic vessels within the Glisson sheath. Here it passes through the peribiliary plexus, the second site important in liver lymph formation. The principal role of this plexus in the normal liver should be sought in the opportunity it provides for secondary modification of liver lymph composition by exchange of soluble components between bile, lymph, and blood."

The high rate of flow of hepatic lymph coupled

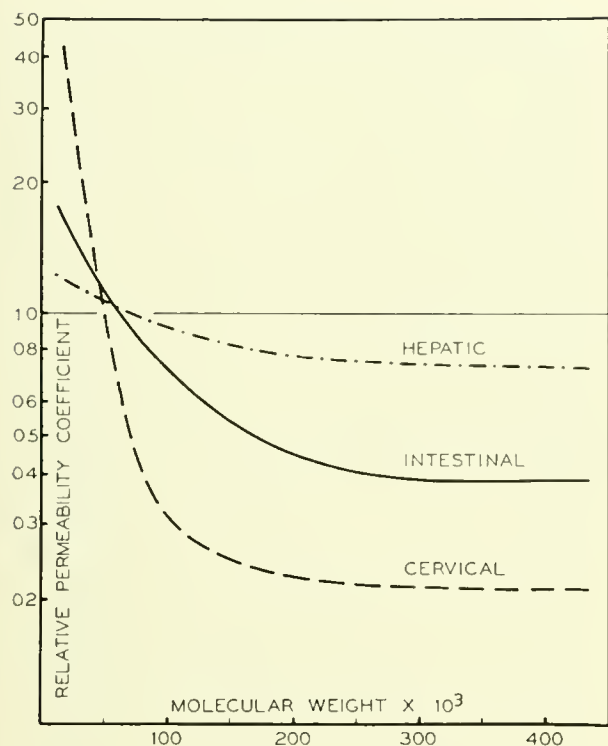


FIG. 4. Curves illustrating relative permeability coefficients for dextrans of different molecular weights. Relative permeability coefficient is ratio of dextran between lymph and plasma divided by ratio of albumin between lymph and plasma. See (141).

with its high protein concentration emphasized the importance of the hepatic lymph system in the turnover of plasma volume and plasma proteins. Little or no new protein, as such, is added to lymph in the liver (234), and the large amount of protein is that which has leaked from blood capillaries and sinusoids. Nix *et al.* (157, 158) estimated that, in the anesthetized dog, the volume of lymph collected from the liver, intestine, and thoracic duct was equivalent in 24 hours to 47, 39, and 95 per cent, respectively, of the estimated plasma volume. They found, as have others, that more than half of the total circulating plasma proteins passes through the thoracic duct daily. When they produced hepatovenous congestion or cirrhosis, the flow of hepatic lymph was two to five times that found in normal dogs. The equivalent of 70 to 207 per cent of the total circulating plasma protein passed through the liver lymphatics in 24 hours. Likewise, Friedman *et al.* (78) collected hepatic lymph from the rat in chronic experiments and reported an average flow of 1.5 ml in 12 hours (12 rats). This rate of flow was increased to an average of 5.1 ml in 12 hours (6 rats) following biliary obstruction.

The role of liver lymphatics in the problem of ascites is discussed by Yoffey & Courtice (234). They point out that in the shifts of fluid which take place when ascites develops, three major sets of lymphatics are involved: lymphatics of the alimentary tract, liver lymphatics, and lymphatics of the diaphragm. All three are capable of carrying very large volumes of lymph, much greater than lymphatics from any other region of the body. Only in extreme circumstances and in the presence of severe disease does gross ascites become evident. Baggenstoss & Cain (10, 11) studied the relationship of hepatic hilar lymphatics to ascites in man. In various conditions associated with ascites, they found these structures increased in size and number when ascites was caused by cirrhosis of the liver or congestive heart failure but not when it was caused by neoplastic involvement of the peritoneum or by renal disease. Other clinical and pathologic conditions associated with ascites which revealed an increase in lymphatic vessels at the hilus were lupus erythematosus, fatal virus hepatitis, and massive liver involvement by neoplasms.

Pulmonary Lymphatics and Edema

There is a very large literature on the anatomy and pathology of the pulmonary lymphatic system but there is comparatively little information on the function of the widespread lymph vessels in the lungs. Warren & Drinker (216) were the first to collect lung lymph in 1942 when they succeeded in cannulating a large lymphatic in the anterior mediastinum of dogs. In 18 animals, they reported an average lymph flow of 1.1 ml per hour and an average protein concentration of 3.7 g per 100 ml. As they realized, their experiments were subject to the criticism that the thorax was open and the usual intrathoracic pressure absent. To obviate this difficulty, they and subsequent investigators turned to collection of lymph from the right duct. This procedure, although eliminating the above objection, introduces other variables. The right duct, as usually cannulated in the dog for lymphatic studies, not only drains the lungs but also carries lymph from the heart, right side of the thorax, and part of the convex surface of the liver. It is thus difficult to quantify the contribution of the lungs to total right duct lymph flow. However, since the contribution from thorax and liver are small, it is probably valid to assume with Drinker (60) that "in the quiescent, anesthetized dog the amount of lymph collected from the right duct expresses the lymph delivery from the contracting heart and moving lungs. If cardiac activity is kept reasonably constant, the quota of right

duct lymph arising from the heart is constant, and variation in output reflects conditions in the lungs."

A second variable is introduced by the occasional occurrence of anastomotic connections with the thoracic duct and thus free flow between the two ducts. Freeman (76) found anastomotic connections in 12 out of 25 carefully injected and examined animals. In the living animal, the presence of anastomotic connections is obvious if right duct lymph is milky rather than clear or becomes milky and increases in rate of flow after pressure upon the abdomen, a maneuver which is very effective in increasing flow from the thoracic duct but not from the right duct. Drinker (60) also suggested that shifting from natural breathing to artificial respiration through a tracheal cannula was a useful test, since artificial respiration increases right duct flow but reduces thoracic duct flow. Further tests can be made by introducing T-1824 dye into one of the lungs via a long catheter or by injecting the dye into the paw or a leg lymphatic. The former procedure results in coloring only right duct lymph if no anastomotic connections are present; the second procedure results in coloring only thoracic duct lymph. Using these tests, our experience has been that fewer than 20 per cent of dogs show functional anastomotic connections.

It is interesting that, in spite of the difficulties described as inherent in the study of right duct lymph, estimations of its flow and protein concentration are not too different from those originally reported by Warren and Drinker for lymph collected from the mediastinal lymph duct, and the protein concentrations are similar to those found in leg and cervical lymph. Thus Courtice (47) found that the average flow from the right lymph ducts of dogs was 2.3 ml per hour and the average protein concentration was 3.7 per cent, levels similar to those found in our laboratory (197). As Yoffey & Courtice (234) point out this would amount to about 2 g of protein daily or 3.6 per cent of the total circulating plasma proteins. The lymph flow is small in terms of the rich blood supply of the lungs. It should be borne in mind, however, that these experiments were done on anesthetized dogs in the supine position and levels of flow and concentration may only at best reflect minimum values.

The pulmonary circulation is a low pressure system and pulmonary capillary pressure is ordinarily less than plasma colloid osmotic pressure, a situation conducive to "dry" lungs. According to the Starling principle, edema would be expected to occur either when capillary filtration pressure was high or protein concentration reduced. Paine *et al.* (163), using the

heart-lung preparation, showed this to be true in experiments in which *a)* they lowered the plasma proteins by plasmaphoresis or by replacement with Locke's solution, and *b)* they elevated hydrostatic pressures by imposing a left ventricular overload. The onset and progression of pulmonary edema were always attended by an increase in the flow of lymph from the right thoracic duct. They conclude that measurement of an increased pulmonary lymph flow is a reliable indicator of the presence of pulmonary edema. Uhley *et al.* (210) and Rabin & Meyer (176) also studied the relationship between pulmonary hypertension, lymph flow, and edema. The former investigators devised a technique to collect pulmonary lymph flow more completely. Instead of cannulating the right lymphatic duct, they create a chamber within the right external jugular vein which traps lymph between the outside of a tube secured in the vein and the vein wall. Lymph is removed from the chamber by a polyethylene catheter. In 13 anesthetized, open-chest dogs under artificial respiration they found average lymph flow to be 0.3 ml per hour. This value is considerably less than that found by others, as indicated above. Elevation of pulmonary venous pressure to 30 mm Hg by introduction of a balloon into the left atrium resulted in an increase in lymph flow to an average of 1.14 ml per hour, the rise occurring about 15 min after inflation of the balloon. After maintenance of elevated pulmonary venous pressure and progressive increase of lymphatic flow for approximately 30 min, critical pulmonary edema ensued. The protein content of lymph paralleled lymph flow. Both increased lymph flow and pulmonary edema were generally promptly decreased with relief of the high pulmonary venous pressures. The authors conclude that the small absolute increase in right duct lymph suggests that lymphatics were unable to function significantly to relieve the acute pulmonary edema. Rabin and Meyer raised left atrial pressures by means of previously appropriately placed snares and found that, with this method, an acute elevation of left atrial pressure could be precisely controlled at any desired level up to a mean of 60 mm Hg in dogs with an intact thorax. Right lymphatic duct flow did not increase at acutely elevated left atrial mean pressures below 25 mm Hg, whereas flow increased 3- to 4-fold at mean pressures above 25 mm Hg. The total amount of lymph at maximum flow, however, was only 0.3 ml per min. Lymph flow remained elevated for as long as 1 hour after left atrial pressure was restored to normal. Pulmonary edema did not occur readily when left atrial mean pressure

was elevated only slightly above plasma oncotic pressure. It was observed only after a considerable elevation of left atrial pressure, above plasma oncotic pressure, was maintained for a period of one-half hour or more. Chronic elevation of left atrial pressure was achieved in 15 dogs. Left atrial mean pressure varied from 10 to 23 mm Hg. The dogs were followed for 10 months. Right lymphatic flow did not increase at chronically elevated mean pressure below 25 mm Hg. They did not study flow at higher pressures because they were unable to sustain left atrial mean pressure above 25 mm Hg in any dog in the chronic group. The animals that were brought to left atrial mean pressure between 30 to 40 mm Hg, and in which these high levels were presumably maintained, were found dead in their cages with pulmonary edema 1 to 2 days after the snare was tightened.

Drinker, while admitting that hemodynamic changes might be responsible for pulmonary edema, stressed the importance of changes in capillary permeability due to anoxia (60). He believed that "increased pressure in the pulmonary capillaries does not readily cause recognizable pulmonary edema unless coupled with heightened permeability, most frequently due to anoxia." His conclusions were based on a variety of experiments by him and his group (65, 216, 217). Thus, forced breathing of dogs against resistance without hypoxia did not cause pulmonary edema, although right duct lymph flow was augmented. On the other hand, when anoxia was present under the same circumstances, increased lymph flow and pulmonary edema were evident. Increased capillary filtration, according to Drinker, results in accumulation of fluid in the alveoli, interfering with oxygen uptake. A vicious cycle is set up as the hypoxia further increases capillary permeability and filtration. Courtice & Korner (48), on the other hand, failed to observe pulmonary edema when they made animals breathe a mixture containing 11 per cent oxygen. They believe that the results of the Drinker group can be equally well explained by postulating an increase in filtration pressure rather than changes in capillary permeability. There is considerable evidence to indicate that the permeability of systemic capillaries does not change at the levels of anoxia produced in the Drinker and in the Courtice and Korner experiments, and the latter correctly conclude that there is no evidence to indicate that the permeability characteristics of the pulmonary capillaries are different with respect to anoxia. Courtice and Korner gave large infusions of Ringer-Locke's solution to rabbits breathing low oxygen. The presence of anoxia led to edema

at a lower level of infusion than when anoxia was not present. The authors believe that this effect can be explained by the hemodynamic changes observed (decrease in cardiac output, systemic vasoconstriction, etc.) without postulating an increase in permeability. It may be pertinent in this connection, however, that Fishman *et al.* (71) recently reported that acute anoxia in human subjects produces a rise in cardiac output and that significant changes in pulmonary arterial pressure (average 7 mm Hg) are not found except when the arterial blood oxygen saturation is below 85 per cent. It also appears that acute hypoxia does not affect the thoracic blood volume (80).

The conclusions of Courtice and Yoffey should also perhaps be modified in light of more recent findings in our laboratory (197). We injected radioactive iodinated serum albumin and dextran fractions of average molecular weights of 51,000 to 255,000 into dogs anesthetized with Nembutal and followed concentration changes in plasma and thoracic and right duct lymphs for 4 to 6 hours. At this time, when a "steady state" had been established between plasma and lymph, we infused 40 ml per kg of 5 per cent serum albumin in 0.9 per cent saline. This resulted in a significant and striking increase in the concentration of the injected radioactive iodinated albumin and dextrans in right duct and thoracic duct lymph in spite of increased lymph flows. We interpreted these results (and earlier ones) to be the result of "stretching" of capillary pores as a result of raised hydrostatic pressure resulting from the expanded blood volume. It is conceivable that the hypoxia in Courtice and Korner's experiments may have served to exaggerate this phenomenon of the capillary wall. It is interesting, in this connection, that the possibility of pore stretching was suggested by Casten & Kistler (40) as an explanation of the acute pulmonary edema which they observed in mice and rats following blast injury and irradiation. They hypothesized: "The intercellular cement substance of capillary walls is postulated to consist of processes having elastic properties that tie the cell walls together. These processes are assumed to be normally under tension. If the intracapillary pressure increases, but remains below a critical value, the tension of the intercellular processes may be still sufficient to hold the cell mosaic tightly together and prevent gross fluid leakage. If the internal pressure exceeds this critical value, then the elastic processes may be stretched to a degree which causes the cell mosaic to be separated, and thereby permit gross fluid effusion to occur. With still greater internal pressure, the processes may be stretched beyond their elastic

limit, hereby producing an irreversible damage to the capillary wall. It is assumed that in the extravasation stage following acute radiation damage, the elasticity and the stretchability of these processes are greatly reduced."

It should be obvious from the brief review given that, in discussing the pathogenesis of pulmonary edema, we are concerned with a syndrome, like circulatory shock, in which many factors may be operative. In an individual case, a single factor may produce indeterminable effects unless it is very powerful. On the other hand, several factors may combine to produce the syndrome at a threshold lower than that necessary for each to act singly. In the final analysis we must assume that in the healthy animal, fluid and proteins which leak from the capillaries are drained off as an equal amount of lymph. Pulmonary edema arises when capillary filtration exceeds the point where the lymphatic drainage is adequate to maintain the relatively "dry" state of pulmonary tissue. This concept, that pulmonary edema results from a relative deficiency in lymph drainage is further supported by the experiments of Földi and his collaborators (75). They studied dogs in which they had experimentally produced mitral insufficiency, mitral stenosis, or bilateral vagal section and ligated the right and thoracic lymph ducts and lymph nodes of the anterior mediastinum. Only tying off the lymphatic supply failed to produce edema as did each experimental procedure under control conditions. When the procedure was combined with lymphatic ligation, however, edema ensued in most animals. Failure to occur under the combined procedure was correlated with lack of lymph congestion presumably to incomplete cutting off of lymph drainage.

Cardiac

The lymphatic supply of the myocardium was first described by Rudbeck in 1653 and has been debated ever since, particularly as to whether myocardial lymphatic capillaries exist. Patek (167) described three plexuses, subendocardial, myocardial, and subepicardial. The subendocardial vessels comprise capillaries in a single plane which drain into the myocardial plexus, a profuse system of interconnected capillaries. According to Patek, there were no efferent lymphatics but only anastomoses with the subepicardial system. Rusznyák *et al.* (188), however, review more recent work of Zhemcherzhnikova and Zhdanov showing that "the musculature of the ventricles in man contains reticularly arranged true lymphatic capillaries.

The loops of these capillaries are situated along the fasciculated muscles." According to these workers, the lymphatic system of the epicardium consists of a double, intercommunicating deep and superficial plexus. The efferent lymphatics are chiefly situated subepicardially, i.e., on the surface, and follow the branches of the coronary artery. The lymphatic trunks of the anterior surfaces of the two ventricles unite to form two lymphatics which run in the anterior longitudinal sulcus from the apex to the base of the heart. The lymphatic which unites the lymph vessels of the posterior surface of the left ventricle runs in the posterior longitudinal sulcus and reaches the anterior surface of the heart in the coronary sulcus. Uniting below the left auricle, these lymphatics form the heart's main collecting lymph vessel which drains into a bifurcation or laterotracheal lymph node. The lymphatics of the posterior and part of the anterior aspect of the right ventricle unite in the right efferent main lymphatic trunk which starts in the posterior longitudinal sulcus, passes over to the anterior surface of the aorta and runs along the surface of the right auricle to the cranial mediastinal lymph node which usually lies on the aortic arch at the origin of the left common carotid artery.

Miller *et al.* (146) have recently raised the question as to whether lymphatic vessels exist in the heart valves of the dog. They examined mitral valves in three groups of dogs: 1) stock dogs killed during the course of other laboratory experiments, 2) "sham"-operated dogs, and 3) dogs in which surgical obstruction of cardiac lymphatic drainage was produced and which were then killed at varying periods of time after surgery. Only an occasional thin-walled channel was found on histological study in the first two groups. However, numerous channels, presumed to be lymphatics, appeared in animals with obstructed lymph flow. The authors believe that interference with lymph flow may play a direct role in heart valve scarring and may provide an additional clue to the mechanism of progressive valvular fibrosis in the years following an inflammatory insult (such as rheumatic valvulitis). These authors also reported ventricular endomyocardial pathology produced by chronic cardiac lymphatic obstruction in the dog (145). Their results are similar to those previously described by Rusznyák (187) who reported many variations in the anatomy of the cardiac lymphatic system. They did not, however, find cardiac lymphatics entering the thoracic duct as Rusznyák reported. They found interstitial edema most often with dilatation of lymph capillaries. Disseminated focal necrosis in the myocardium was pres-

ent in 3 dogs and left ventricular subendocardial hemorrhages in 7 of 17 dogs. They describe other changes and point out the merit of further investigation of cardiac lymphatics and the relationships of disturbances of their function to pathologic states. Rusznyák and co-workers have also described the results of similar experiments done by their group. They report in detail the electrocardiographic changes seen after cardiac lymphatic obstruction and after ligation of the coronary sinus and cardiac lymph nodes. They also emphasize the possibility that lymphatic congestion may play an important role in the pathogenesis of mitral stenosis and other cardiac diseases.

Drinker and his colleagues (64) are the only group to date who have collected and studied cardiac lymph. They reported measurements of flow in 10 dogs as varying between 0.31 to 1.65 ml per hour (average 0.8 ml/hour) with no correlation between dog weight, heart weight, blood pressure, and lymph flow. Since only one lymphatic was cannulated and since there are usually two main efferent trunks, the total flow was probably approximately twice the values obtained. This would mean that about 60 to 70 per cent of the total right lymph duct flow comes from the heart. The lymph always contained a relatively high concentration of protein. The average for 18 dogs was 3.69 per cent with a range between 2.50 to 4.73 per cent. Since right duct lymph contains approximately the same concentration, this suggests that cardiac and lung lymph have about the same concentration of protein. This is also supported by the values obtained by Warren & Drinker (216) in collection from a large lymphatic in the anterior mediastinum. Thus there is in the heart, as in all other tissues studied, a continuous leakage of protein from the capillaries and the rhythmic contractions of the cardiac muscle insure its rapid removal by the extensive lymphatic plexuses. These investigators also found that cardiac lymph flow increased after the injection of epinephrine and ephedrine, the rise appearing to be correlated to the increased cardiac work. Experiments with a Starling heart-lung preparation designed to simulate exercise (increased input and peripheral resistance and addition of epinephrine) showed a marked increase in lymph flow to 24 ml per hour. As Yoffey & Courtice (234) point out, even if we accept a figure of 18 ml per hour, a hound engaged in a 12 hours' chase would be putting out 216 ml of cardiac lymph. With a heart weight of 91 g, this would mean 2.4 ml of lymph per g of heart during the 12 hours.

Renal

Although a relatively extensive literature has accumulated concerning the distribution of kidney lymphatics and their possible role in clinical disorders (88), the physiological role of renal lymph is less well documented. This is due to the difficulty in cannulating the vessels because of their location and extremely small size. The main hilar trunks are particularly inaccessible to cannulation, whereas capsular lymphatics, although more accessible, are quite small and difficult to cannulate. This has led some investigators to the highly unphysiologic compromise of eviscerating animals and collecting thoracic-duct lymph on the assumption that this lymph was now derived solely from the kidney.

The first physiological experiments on renal lymphatics were made by Ludwig & Sawarykin (129), who showed that ligation of a ureter was followed by dilatation of efferent renal lymphatics. They did not study lymph flow or composition under these conditions, but their experiments form the basis of a more recent elaborate study by Babics and his collaborators (7, 8), whose work will be discussed later. Sugerman *et al.* (204) were probably the first to collect renal lymph directly and begin its characterization in dogs. They cannulated both capsular and hilar lymphatic trunks and reported a wide fluctuation in flow and protein concentration. The slower the lymph flow, the greater was the concentration of protein. Their average figure for flow from 11 dogs was 0.0232 g per min (1.392 g/hour) and for protein concentration 1.84 g per cent. Of interest was the finding of a higher average urea concentration in renal lymph (69.7 mg %) than in plasma (53.1 mg %). In some animals, the lymph urea concentration was considerably higher than that in plasma of the renal artery or vein. These findings posed two questions: 1) Do the renal lymphatics drain only the larger collecting ducts of the kidney, thus accounting for the high urea content of its lymph? 2) Is renal lymph derived from tubular reabsorbed fluid, the blood plasma, or from both types of fluid? Attempts to answer these questions were made by Kaplan *et al.* (107) who determined and compared the glucose content of renal and cervical lymph samples as well as their inulin content during an intravenous infusion of inulin. The average concentration of glucose in 8 renal lymph samples was 92.7 mg per cent and 101.9 mg per cent in 8 cervical lymph samples. They concluded that this high glucose concentration in renal lymph suggests that renal lymph could not be derived exclusively from the relatively sugar-

free fluid contained in the larger collecting ducts of the kidney. The average concentration of inulin in renal lymph from 8 dogs was found to be 82.5 mg per cent or 94 per cent of the plasma concentration. The authors considered these results as evidence that the composition of renal lymph is determined by the character of both tubular reabsorbed fluid and renal blood plasma. If it were derived exclusively from the renal tubular reabsorbed fluid, its inulin content would be practically nil and if it were derived exclusively from renal blood plasma, its inulin content would be equal to that present in plasma.

Swann and his colleagues (205) reported measurements on renal capsular lymph from 5 dogs. Lymph flow was between 0.1 to 0.3 ml per hour. They also found urea concentration of renal lymph to be higher than plasma and glucose concentration to be lower. They found total protein content to be quite constant at about 3.2 g per cent, about half that present in plasma, and failed to observe the inverse relation of protein content to lymph flow reported by Sugerman *et al.* Electrophoretic separation of the proteins showed that their distribution in lymph was similar to that in plasma.

About 5 years ago, my colleague, Dr. S. J. LeBrie, and I began a comprehensive study of renal lymph as part of a general study of lymph and lymphatics. We have collected renal capsular lymph in a variety of experimental situations which will be detailed below. We have found the lymph flow to be quite variable and unrelated to sex, age, or size of the animal. The average control flow for 63 dogs studied up to the present time is 0.0128 ml per min or 0.768 ml per hour. Total protein concentration for 40 dogs averages 2.76 g per 100 ml or about half of plasma concentration.

We find protein distribution to be similar to that of plasma, confirming the findings of Swann *et al.* All plasma proteins, including fibrinogen, are present in renal lymph. Potassium concentrations appear to be identical in lymph and plasma. We previously reported (121) that the average lymph sodium concentration for 30 dogs was 11.3 per cent higher than in plasma. Addition of more data and refinement of experimental procedures suggests that this value may be too high and the difference may or may not be significant. Limited data on osmotic pressure also have been equivocal. Data on 30 dogs show lymph chloride concentration to average 13 per cent higher than plasma, a difference which is statistically significant. We have some indication that bicarbonate concentration is lower in lymph than in plasma. Obviously

we need more data to clarify the situation with respect to these constituents. These data are being accumulated.

It is of interest to compare renal lymph flow with urine flow in the same kidney. It is reasonable to assume that there are at least ten lymphatics draining each kidney. Using the average flow which we obtained from one lymphatic, the average total lymph flow from both kidneys would amount to 0.128 ml per min, which is approximately half of the average amount of urine flow. In some animals with high lymph flows, the amount of capsular lymph drained equals the amount of urine formed. Similar admittedly rough calculations for protein yield a value of 10.2 g of protein returned to plasma per day via capsular lymphatics of both kidneys. It should be emphasized that these are average values for the anesthetized dog and probably reflect minimum levels.

Renal lymph flow is markedly increased by raising venous pressures. This was first shown by Schmidt & Hayman (195) and later confirmed by Katz & Cockett (109) and by us (123). Schmidt and Hayman analyzed the changes in thoracic duct lymph flow in eviscerated, hepatectomized, and uninephrectomized dogs following ligation of the remaining functional renal vein. They concluded that the increase in renal lymph flow was responsible for the observed rise in thoracic duct lymph flow when venous pressure was raised. Katz and Cockett likewise concluded that changes in renal lymph were responsible for changes in thoracic duct lymph which they observed. They observed an increase in thoracic duct lymph flow and sodium concentration as well as a decrease in urinary flow and sodium concentration when venous pressure was raised. The changes occurred only when the kidneys were intact. Haddy and his colleagues (94), in experiments designed to study pressure and flow relationships in the kidney, also reported that renal lymph flow increased as a function of venous pressure. In our experiments, we collected capsular lymph and raised the venous pressure by partially occluding the inferior vena cava with a balloon catheter. We also measured protein and electrolyte changes. Renal lymph flow increased about five times during the periods of increased venous pressure and the flow from one lymphatic equaled and often exceeded urine flow from the same kidney. Electrolytes and protein levels changed proportionately except at high venous pressure levels (30–35 cm H₂O) when disproportionately high levels of protein were found in renal lymph.

In discussing the significance of the changes in lymph

phatic flow and composition produced by increased venous pressure, we suggested that they might have some bearing on the problem of plasma volume increase and sodium retention in congestive heart failure, a syndrome in which venous pressures not infrequently approximate the high levels used in our study. We pointed out that under conditions of significantly increased venous pressure the total lymph flow from both kidneys may amount to as much as 2400 ml per 24 hours. This would represent a total of ± 379 meq of sodium not excreted by the kidneys but retained by the lymphatic system. A study of kidney lymph flow in postural proteinuria might also be of interest. Bull (32) believes that "A rise in pressure in the inferior vena cava is produced by compression of the vessel against the spine by the posterior surface of the liver. This pressure is conducted back to the kidney, inducing passive congestion and proteinuria. The compression occurs when the subject is in a lordotic posture and when the anterior surface of the liver rotates inferiorly. This rotation of the liver normally occurs when the subject is lordotic and is maximal in the erect lordotic posture." Goodwin & Kaufman (89) suggest the possibility of thoracic duct or cisterna chyli lymphatic obstruction and retrograde lymph flow as a possible explanation of the proteinuria and cite the report of Lowgren (128) as suggesting this explanation.

If we agree that one of the primary functions of the lymphatic system is to return to the vascular system those proteins and other large molecules which have leaked out of the blood capillaries, our accumulated data emphasize that kidney lymphatics are no exception. This is a function of considerable importance for the kidney. Maintenance of a relatively low concentration of interstitial protein is necessary for the maintenance of the countercurrent action in the kidney. This concept visualizes the vasa recta as a countercurrent exchanger carrying off salt and water. Gottschalk & Mylle (90) believe the efficiency of the countercurrent exchange in the vasa recta to be critical, "for they probably remove not only the blood entering the medulla, but also the water that diffuses from the thin descending limbs of the loops of Henle and the collecting ducts. This water, with solute isosmotic for the particular level of the medulla, presumably moves into the vasa recta because of the gradient of its chemical potential established by the colloid osmotic pressure of the plasma proteins, since the hydrostatic pressure in the capillaries and interstitium are the same." The gradient of colloid osmotic pressure between the interstitium and the plasma can be main-

tained only if the colloid osmotic pressure of the interstitium is kept well below that of the plasma. We believe that this is an important function of renal lymphatics, the maintenance of a relatively low oncotic pressure in the interstitium and thus the establishment of a gradient with the higher oncotic pressure within the vasa recta. Thus, as the lymphatics carry off plasma protein that has pooled in the medullary interstitium, the colloid osmotic pressure of these proteins draws water with a higher or lower solute concentration, depending upon the level of the countercurrent gradient at which the lymph is formed. The medullary and cortical lymph passes into lymph collecting trunks, mixing the two and thus reducing the electrolyte concentration and osmolarity. Some collecting trunks leave the kidney through the cortex while others follow the path of the artery and vein to the hilus. When renal venous pressure is increased, more protein is lost in both cortex and medulla due to increased hydrostatic pressure. Thus, although filtration of protein increases as does water, the concentration of filtered electrolytes does not increase over control values. We assume that filtered electrolytes from cortical capillaries are isosmotic with both plasma and cortical interstitial tissue, while filtered electrolytes from the vasa recta are hyperosmotic to plasma but isosmotic to the countercurrent gradient in which they lie. Thus, if these fluids are mixed, one might expect the concentration of sodium in milliequivalents per liter to remain unchanged. This is essentially what we find.

In terms of the above discussion, we would expect ligation or obstruction of lymphatic outflow to produce edema and significantly alter kidney function. Kaiserling & Soostmeyer (105) succeeded in tracing the lymphatic vessels to the main hilar branch in rabbits and in tying it off. The kidney began to swell immediately and had reached double its original size within 10 to 15 min as a result of massive interstitial edema. There was a marked increase in urinary output on the side with lymphatic ligation and, significantly, the urine from the experimental side had a specific gravity of 1.013, whereas the control side had a specific activity of 1.035. Later, the urine flow diminished, proteinuria was present, and the kidney and its parenchymal cells degenerated 8 to 10 days after the lymphatics were ligated.

These and other similar studies and their implications are discussed at length by Babics (7, 8) and Rusznyák *et al.* (189).

Earlier mention was made of the fact that the first experiments on renal lymph were those of Ludwig &

Sawarykin (129) who noticed that ligation of a ureter was followed by dilatation of the efferent renal lymphatics. Similar observations have since been made by many investigators (88, 153, 154, and LeBrie and Mayerson, unpublished) who have also shown that renal lymph flow is significantly increased. Katz (108) measured renal lymphatic pressure in two dogs with pyelonephritis and found the pressures to rise when either the renal vein or the ureters were compressed. It is apparent that the renal parenchyma shows no significant changes for a number of weeks after the experimental ligation of the ureter; the only histopathological symptoms that can be observed for a considerable time are a high degree of interstitial edema and marked dilatation of lymphatics. Babics & Rényi-Vámos (7) ascribe the survival and continued performance of the hydronephrotic kidney to the fact that urine passes from the renal pelvis into the interstitial space of the kidney where it is continuously absorbed into lymphatics. Histamine is presumed to be liberated, increasing capillary permeability and transudation of protein. This protein, too, is carried away by the lymphatics. If, on the other hand, the lymphatics are also tied off, necrosis is seen within a few days [see Babics & Rényi-Vámos (7) and Rusznyák *et al.* (189) for detailed discussion].

The general effect of diuretics is to increase renal lymph flow. Reference has been made to the work of Schmidt and Hayman who showed this to be true for phosphate, sodium chloride, and caffeine. We have collected renal capsular lymph in dogs during diuresis produced by sodium chloride, urea, mannitol, and mercury (LeBrie and Mayerson, unpublished). Under the conditions of our experiments, we obtained the most marked diuresis with urea and mannitol and the least with mercury. Mannitol produced the greatest increase in lymph flow (average 10 dogs = 587%), while mercury and urea produced the least (Hg, 15 dogs, 42%; urea, 7 dogs, 41%). These experiments are being continued and attempts are being made to elucidate the mechanism of the changes in flow, electrolyte and protein concentration, and to explain the differences seen with the different diuretics.

We have also studied the influence of uranium-nitrate injury on the flow and composition of renal lymph (122). Lymph flow was increased approximately 15 times in the experimental animals. Likewise, the increase in lymph flow with mannitol infusion was about twice as great in the experimental animals (1000% increase) as in control animals (542% increase). The experimental animals showed a significant proteinuria and decreased urine flows,

and the data appear to be consistent with the histologic findings of primary damage to the distal segment of the proximal tubule.

The finding of an increased lymph flow when ureters are obstructed and diuretics are administered has given rise to the concept emphasized in clinical literature, that the renal lymphatics act as a "safety-valve" mechanism, capable of taking the extra load from the kidney under conditions of overload. Backflow from the kidney pelvis to the renal lymphatics has also been suggested by experiments of Murphy & Myint (153) and Goodwin & Kaufman (89). The former introduced glucose and the dye T-1824 into the renal pelvis and found these substances earlier and in greater concentration in lymph of the cisterna chyli than in renal or femoral blood. The latter injected radioactive Diodrast into the renal pelvis during ureteral occlusion and found the same radioactivity at the same time in thoracic duct lymph and in the control vascular area. More work along these lines is needed, particularly defining the mechanisms involved and the effects of pyelolymphatic backflow in kidney disease. However, it may be pertinent to emphasize, as has been previously suggested, that the general function of the lymphatic system is to act as a "safety valve" and as an accessory circulation, clearing the interstitium of excess substances which leak out of or are not absorbed directly into the blood stream and returning them to the blood circulation. This is not a peculiar or special function of renal lymphatics. Thus, an overload of the circulatory capacity as produced by a large intravenous infusion results in an increased lymph flow, etc. The particular importance of lymph with respect to normal renal function lies in the fact that the oncotic pressure of the interstitium must be kept low in order for the vasa recta to act as a counter-current exchanger. In the absence of adequate lymph drainage the kidney becomes unable to concentrate urine (105).

LYMPH AND LYMPHATICS IN SHOCK

Anaphylactic Shock

Petersen & Levinson (173) found that injection of antigen into dogs resulted in an increased permeability of splanchnic endothelium and subsequent reaction of the hepatic parenchymal cells with the antigen. In further work, Petersen & Hughes (172) showed the injection of egg white into dogs sensitized

to egg albumin to result in an immediate and marked increase in thoracic duct lymph flow with increased concentrations of calcium, amino nitrogen, and magnesium, and decreased concentrations of sodium and potassium. They did not measure proteins. Dragstedt and his colleagues (55-57, 82) reported that, in the dog at least, the vasomotor symptom and death occurring in anaphylactic shock are brought about by the sudden discharge into the circulating blood of a vasodepressor, smooth muscle-stimulating substance which is apparently histamine. They were able to detect this substance in blood and thoracic duct lymph for brief periods of time after the assaulting or shocking dose of serum, and to correlate its appearance with varying grades of severity of the shock in such a way as to indicate that it had a causal relationship to the shock symptoms. More specific results were recently reported by Logan (127) who showed that bovine globulin is a satisfactory antigen for sensitizing rats when given intraperitoneally simultaneously with *Bordetella pertussis* vaccine. Intestinal lymph of animals so sensitized contained increased amounts of histamine when collected 6 min after intravenous injection of the shocking dose. The amount of lymph histamine was roughly proportional to the degree of shock. The rate of lymph flow increased 8 to 25 times during the 12 min immediately after administration of the shocking dose and the lymph contained 0 to 0.02 μg histamine per ml, an amount similar to that in plasma.

The lymphagogue action of histamine is well known and can readily be demonstrated by the intravenous injection of small amounts of the substance (95). This effect has usually been ascribed to dilation and increased permeability of capillaries, although the exact mechanisms involved have never been clearly defined. Ruzsnyák *et al.* (189) review much of the evidence and report experiments done in their own laboratories by Szabó and Magyar. The latter injected a dextran fraction of approximately the same molecular weight as albumin simultaneously with histamine and with Evans blue. In dogs, flow of intestinal and hepatic lymph increased two to three times and remained high; appearance of dextran and dye-labeled albumin in lymph was much sooner as was equilibration between plasma and lymph. The authors believe they have ruled out the factor of increased filtration pressure in favor of increased capillary permeability. Repetition of the same experiments in cats gave entirely negative results, i.e., no increased lymph flow or accelerated equilibration. The authors explain these differences as being due

to the fact that in the dog not only the capillaries and small veins but also the arterioles are dilated by histamine (and only the larger visible arteries constricted), while in the cat this constrictor effect begins more peripherally in the arterioles. The authors take issue with the assumption by Krogh (117) that dilation of capillaries leads to increased permeability, since capillaries dilate in the cat quite as much as in the dog without showing increased permeability.

Changes in blood coagulability are among the important findings in the anaphylactic reaction (67, 104) and result from the release of heparin from the liver. The possibility that this substance may be transported from the liver to the blood stream by way of the thoracic duct was first suggested by Gley (87) who found that ligation of the liver lymphatics prevented the incoagulability of blood following peptone shock. White & Woodward (228-230) showed that the incoagulability of thoracic duct lymph following an anaphylactic or peptone-induced shock is due to heparin and that the main portal of entry for this substance into the blood stream is via the thoracic duct from the liver. The concentration of heparin in lymph in these situations was greater than in arterial or hepatic venous blood and it was frequently present only in thoracic duct lymph. When heparin was given intravenously the concentration of heparin was the same in thoracic duct lymph and in plasma. Furthermore, heparin did not appear in cervical or right duct lymph unless it first appeared in blood. Removal of the liver prevented the appearance of heparin in peptone-shocked dogs. These findings confirm the liver as being the origin of heparin under these circumstances. Heparin was not released into thoracic duct lymph or blood during a hemorrhage-induced shock, thus ruling out hypotension as a factor in the heparin release. It is suggested that the release of the heparin may depend upon limited cellular reactions and not upon general cellular activity.

Traumatic Shock

There has been considerable interest in studying the participation of the lymphatic system in traumatic shock. These studies have taken different forms. The Hungarian workers (188) have done a considerable amount of work in which they have measured lymph flows from various areas and used the composition of lymph as a measure of capillary permeability. There has been a recurrent interest in the presence or absence in lymph of a "toxic" substance which may or may not have come from the plasma.

The question as to whether capillary permeability is altered in shock has been a hardy perennial. A detailed discussion of this topic would be out of place at this point. It is, however, appropriate to call attention to the studies of the Hungarian group referred to above in which they have made extensive observations on the role of lymph and lymphatics in dogs during and after traumatic shock. They have used the same general approach as we have used (141, 219) of introducing dextrans of molecular weights similar to those of albumin and globulin into the blood stream, following their disappearance from the blood stream and their appearance in lymph from various regions. Since radioisotopes were not available to them, they used the dye, T-1824, which is known to bind onto albumin and thus constitute a label. Their results on control animals resemble in general those which we obtained; albumin or dextran of molecular weight of about 50,000 appeared in thoracic duct lymph within 10 min and, in their experiments, the average dextran concentration was 29 per cent of that in plasma at 15 min and about 75 per cent at 60 to 90 min. In tourniquet shock produced by arresting the circulation of the hind legs for 5 hours, they found a more rapid disappearance of the dextran from the blood stream but a much slower appearance and accumulation in thoracic duct lymph. At 90 min there was only an average of 43 per cent of dextran in the lymph. Lymph flow was considerably reduced. These workers also studied cervical lymph and, while their results were not definitive, it seems reasonably certain that the capillary permeability in peripheral regions was not increased. Attempts to find the reasons for the decreased thoracic duct lymph flow and the delayed appearance of protein and dextran were not successful. It was apparently not due to diminished hepatic-lymph formation or to lymphangiospasm. They interpret the faster disappearance of the dextran from blood as reflecting the increase in capillary permeability in the ischemic area rather than a generalized increase in permeability. One of the group (226) has extended some of the work to hemorrhagic and burn shock and again finds a decreased thoracic duct lymph flow which parallels the severity of the shock. He also interprets his data as denying any generalized increase in capillary permeability.

Since edema is prominent in the ischemic areas, these investigators went on to study the flow of leg lymph and the behavior of albumin and dextran in the hope of ascertaining whether the edema was due to an inability of the lymphatic system to cope with

an increased tissue fluid formation or whether there was injury to the lymphatics caused by the ligatures. Although the small lymph flow in leg lymphatics precluded quantitative data, there was no question of the direction of change and that protein leakage was increased in the ischemic area. The increased lymph flow argued against lymphatic injury or occlusion as factors in the edema production.

The occurrence of a vasoconstrictor substance in blood during shock induced by trauma, hemorrhage, and burns was reported in dogs by Page (161) and denied for ischemic compression shock (91). Rapport *et al.* (180) also reported the occurrence of a "toxic factor" in tourniquet shock in rabbits.

In 1943, Blalock (19) reported the results of experiments in which he produced crush injury in anesthetized dogs by applying a press to a hind leg. Thoracic duct lymph collected from these dogs after removal of the pressure and injected into other dogs brought on a decrease in blood pressure and death of some of the animals. Less marked results were obtained when trauma was produced by striking the legs with a blunt instrument. Blalock explained his results as due to the presence of a toxic substance in lymph of the traumatized animals. Katzenstein *et al.* (110) reported similar results in shock produced by tourniquets around the hind legs. These authors appreciated the possible vasodepressor effects of large doses of Nembutal which they used but showed that when narcosis was controlled to avoid vaso-depression, injection of thoracic lymph from normal dogs had no effect. In contrast, a fall in blood pressure followed in 50 per cent of the animals injected with lymph of shocked animals. The problem was further studied by Nathanson and his collaborators (155), who devised a method of producing tourniquet shock in dogs which permitted the collection of muscle exudate. They collected the exudate, which accumulated after muscle anoxia, and injected it into the same or recipient dogs (6). Shock was produced in only 25 per cent of the animals tested. The inconsistency of the presence of the toxic factor suggested that the factor was an extraneous agent, not present in the usual cellular constituents and metabolic products found in all muscle exudates, and possibly bacterial in origin. They further showed (235) that the toxic properties of a collection of pooled muscle exudates were contained in a nondialyzable fraction, could be salted out between 0.25 and 0.7 saturation with ammonium sulfate and were, therefore, probably protein in nature. The toxic substances were tentatively classified as an aminooxopeptidase and a

trypsinase which were present in the exudates. Freeman & Schechter (77) tested leg lymph obtained from dogs whose hind legs were traumatized or heated and found that it produced an increase in permeability as judged by leakage of dye when injected into recipient animals. Arterial and venous serum and plasma also contained a similar factor which increased capillary permeability, and the authors concluded that it was likely that the presence in lymph of a substance capable of producing an increase in capillary permeability is dependent upon the appearance, after trauma, of blood plasma in the lymph draining from the extremity. On the other hand, Lindner *et al.* (126) failed to find any evidence of a permeability factor either in lymph or plasma in shock produced by manipulation of the intestine. Their experience was similar to the earlier one reported by Dragstedt & Mead (57), who produced shock by sustained trauma with a padded hammer to one or both hind legs, by trauma to the intestine, or by a combination of the two methods.

Burns

Some work has been done on the study of lymph in burns. Aldrich (2) collected leg lymph from burned, anesthetized dogs and perfused it through rabbit ears. Blood flow as measured by drop rate definitely decreased when lymph from burned animals was used as compared to lymph from healthy dogs. No attempt was made to identify the vasoconstrictor substance.

Glenn and his colleagues, in Drinker's laboratory, studied the changes in lymph composition after leg burns produced with hot water in calves (85, 86, 170). Cervical and leg lymph was followed. Lymph flow in the burned legs was significantly increased as was the protein concentration of the leg lymph. Cervical lymph, however, did not show the increase in protein. Electrophoretic studies showed the occurrence of a new protein in the lymph from the burned leg, a component migrating with half the speed of γ -globulin. Cope & Moore (44) also reported a significant increase in capillary permeability following hot water burns of legs of dogs. They injected radioactive colloidal dyes into the blood stream and measured their appearance in leg, cervical, and thoracic duct lymph before and after the burn. They also injected radioactive bromine, which they found to appear in lymph from the three areas within 5 min and to reach equilibrium with serum in 20 min. In contrast, the colloidal dyes were slower in appearance in

lymph and no equilibrium was established with serum under control conditions. Following the burn, the concentration of radioactive colloids in lymph of the burned leg rose abruptly and approached that encountered after injection of radioactive bromine. The specific activity of protein was actually higher in lymph than in serum after the burn. In confirmation of Glenn *et al.*, they also found that the increased capillary permeability was usually restricted to the burned leg. A rise in colloid concentration in cervical lymph was observed in only one dog.

Permeability Factors

During the last decade, considerable interest has been aroused in the presence in plasma of endogenous substances which, when activated, induce pathological increases in capillary permeability (144). Two classes of natural mediators have been suggested: 1) the pharmacologically active amines, histamine, and hydroxytryptamine; and 2) proteases and products of proteolysis. This latter group includes the proteases of plasma (plasmin, the serum globulin permeability factors, and polypeptides like leukotaxine and bradykinin). The groups overlap in that polypeptides may act as histamine liberators. There is direct and indirect evidence that these substances participate in the mediation of the response to injury, but much more evidence is needed to define their role in the healthy animal and in animals suffering from hemorrhage, burn, or other trauma. It would be interesting to extend the observations of Miles & Wilhelm (144) to other substances, species, and experimental conditions. These investigators showed the presence in the guinea pig of the precursor (pro-PF) and the inhibitor (IPF) of one of the globulin permeability factors, both in intercellular perfusates of skin and in normal lymph from the cervical lymph ducts (143). It appears that the proteins constituting the pro-PF/IPF system of the blood, like other plasma proteins, pass continuously via the extravascular tissues to the lymph, and that the extravascular tissues, including the outer surface of the capillary wall, are bathed in tissue fluid containing pro-PF.

PERMEABILITY OF LYMPHATIC VESSELS

Although a considerable amount of work has been done relative to the permeability of blood vessels, we have very little definitive information regarding

permeability characteristics of lymph vessels. Light microscope studies suggested that lymph and blood capillaries are morphologically similar, a suggestion which has been confirmed by recent studies, particularly those of Casley-Smith & Florey (39a). These authors showed that there were no species differences in lymphatics of mice, guinea pigs, and rats, and that the lymphatics of the ear and the deep lymphatics of the diaphragm and colon were similar. In general, the structure of the lymphatic capillaries and lacunes appeared to be similar to that of blood capillaries. All the lymphatic endothelial cells contained many vesicles and caveolae intracellulares. No fenestrations in the endothelium were seen, but some intercellular junctions were patent, especially in diaphragmatic lacunes. The basement membrane was less regular than that of blood capillaries or of mesothelium and in many places, especially in diaphragmatic lacunes, it appeared to be absent. These results are similar to those of Palay & Karlin (164) and French *et al.* (77a). The absence of a definable basement membrane would not, as Casley-Smith and Florey point out, fully differentiate lymphatic from vascular endothelium, since the endothelium lining large blood vessels may have at best a very tenuous basement membrane. The significance of the absence of fenestrations in the lymphatic endothelium also remains questionable in the absence of definite information as to the importance of their presence in determining permeability characteristics. The significance of their other findings will be discussed further below.

The permeability pattern in lymphatics presents an interesting and challenging problem. It is obvious from the preceding discussion that proteins, chylomicrons, and lymphocytes are normal constituents of lymph as routinely collected from healthy animals. Experimentally, bacteria, viruses, red blood cells, graphite particles, etc. have been shown to penetrate the lymphatic system with no apparent difficulty. Lane Allen (1a) showed that every type of cell which occurs normally in tissue fluid and blood will penetrate lymphatic endothelium. He felt he had identified every cell of the hematopoietic series, except giant cells, in diaphragmatic lymph after intraperitoneal injection of bone-marrow suspensions. Likewise, he found that the entire series of lymphoid cells will enter through lymphatic endothelium. The large amount of literature published before 1956 describing these experiments has been thoroughly reviewed by Yoffey & Courtice (234). The more recent publications will be discussed later.

In spite of the apparent ease with which substances can penetrate into the lymphatic vessels, the available evidence suggests that once these substances are in the lymphatic system, they are retained and eventually find their way into the blood stream via the larger ducts. Thus MacCallum (132a) retroinjected the lymphatics of the diaphragm and failed to force suspended particles back into the peritoneal cavity, except when he used pressures sufficient to rupture the lymphatics. Hudack & McMaster (100a) injected dyes into the ears of mice and studied the escape of these substances from the lymphatics. They reported that poorly diffusible dyes (pontamine sky blue, Chicago blue 6B) which pass with difficulty out of blood capillaries into the tissues, tend to be retained by the lymphatic wall as well, whereas more highly diffusible dyes (trypan red, bromphenol blue, and Neptune blue) pass out with ease. Rusznyák *et al.* (189) have more recently reported similar results using fluorescent dyes (thiazine red, acridine yellow) in intestinal lymphatics of cats. Hudack and McMaster concluded that "all the evidence we have obtained supports the view that permeability of the lymphatic wall resembles the permeability of the capillary wall in its essential features and perhaps in its degree." Drinker & Field (61a) retroinjected lymphatics of the frog web with graphite acacia and found no passage of the graphite particles until rupture resulted from excessive pressure. Pullinger & Florey (175) found that when they injected graphite particles into ear lymphatics of the mouse, the fluid leaked out but the graphite particles remained. Similarly, Lee (124a) found that large particles of centrifuged, dialyzed India ink were retained in lymph vessels, whereas small particles passed through. Courtice & Steinbeck (50a) attempted to evaluate lymphatic permeability by injecting T-1824-labeled plasma proteins intraperitoneally into rabbits and collecting lymph containing the protein from the exteriorized thoracic duct. They found that the injected proteins were almost entirely absorbed by the diaphragmatic lymphatics. In further work (50b) they demonstrated that ligation of the parasternal lymph channels in rabbits, rats, and guinea pigs prevented the dye-labeled protein from reaching the circulation via the thoracic duct, but instead, after entering diaphragmatic and mediastinal lymph channels, it proceeded to leak into the mediastinum and pleural cavities. They concluded from these experiments that lymphatics leaked protein, a conclusion open to question in view of the obviously unnatural conditions of their experiments. Ligation of the parasternal lymph chan-

nels and the resultant increased intralymphatic pressure and distention of the lymph vessels might conceivably permit leakage of substances which ordinarily would be retained within the lymphatic vessels as has been previously shown to be true in earlier work cited above. This has been shown to be true of blood capillaries (197). Furthermore, the fact that Courtice and Steinbeck found no protein leakage when the ducts were not ligated suggests that the lymphatics of the anterior mediastinum, under normal circumstances, will not permit leakage of significant amounts of the protein which is contained by them.

In a recent study (168) we attempted to obtain answers to the questions: *a*) Does the capillary filtrate, once it is in the lymph ducts, empty without loss into the venous circulation or is protein free to pass out of the lymphatic vessels throughout their lengths? *b*) Does any protein pass into the blood capillaries? *c*) Is any considerable amount of protein phagocytized by the reticuloendothelial cells of lymph nodes? Furthermore, to what degree, if any, is lymph shunted to the blood stream through lymph-blood anastomoses without returning via the thoracic duct? Anomalous shunts, consisting of multiple outlets of right and left ducts, have been described as well as shunts between the right and left thoracic ducts in about 15 per cent of dogs (234, 197). One phase of our study involves the cannulation of a leg lymphatic in an anesthetized dog, the infusion into it of substances of different molecular weights, and obtaining and analyzing samples of thoracic duct lymph and plasma. The infused material thus travels through a number of lymph nodes, through lymphatic vessels of different sizes, and through capillaries.

The second approach to the problem is to utilize a preparation developed some years ago by Drinker and his group (63). One afferent and one efferent duct going to and from the popliteal node are isolated and catheterized with polyethylene tubing. All other lymphatics are tied off. Test substances are infused through the node from the afferent side and collections are made on the efferent side. Nodal and systemic plasma are also obtained and analyzed.

When radioactive iodinated albumin is infused into a leg lymphatic, there is a typical, consistent pattern of appearance of the albumin in thoracic duct lymph as shown in figure 5. There is a lag time of approximately 10 min between the start of the infusion into the leg lymphatic and the appearance of measurable amounts of radioactive albumin in thoracic duct lymph. This is followed by an abrupt rise to a plateau which is maintained at an approximately constant

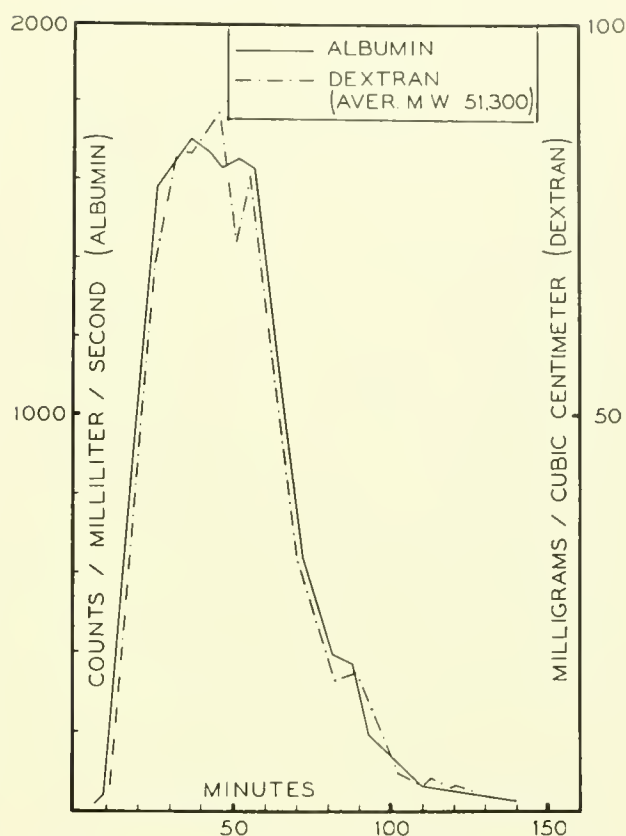


FIG. 5. Concentration of dextran and I^{131} albumin in lymph and plasma. Dextran and I^{131} albumin solutions infused centrally into leg lymphatic of anesthetized dog at zero time at rate of 0.5 ml/min. Infusions of dextran and albumin stopped after 50 min and 0.9% saline infusion started at same rate for next 100 min. All values are corrected for free iodine.

level for the 50-min duration of the albumin infusion and for 10 min of a subsequent saline infusion. At this time, radioactivity in thoracic duct lymph falls sharply and continues to fall until the level approximates zero in about 140 to 150 min. Plasma radioactivity rises to a maximum concentration after 60 to 90 min and remains at this level for the remainder of the experiment. The maximum plasma concentration is less than 0.001 of the thoracic duct lymph concentration during its 50-min plateau period. Figure 5 also shows the similar behavior of dextran of approximately the same average molecular weight as albumin. It is apparent that these infused substances do not leave the lymphatic system and that they return to the circulation primarily by the thoracic duct. Actually less than 3 per cent of the infused material reaches the circulation by routes other than the thoracic duct, except in unusual cases of right and left duct anastomoses. The experiments

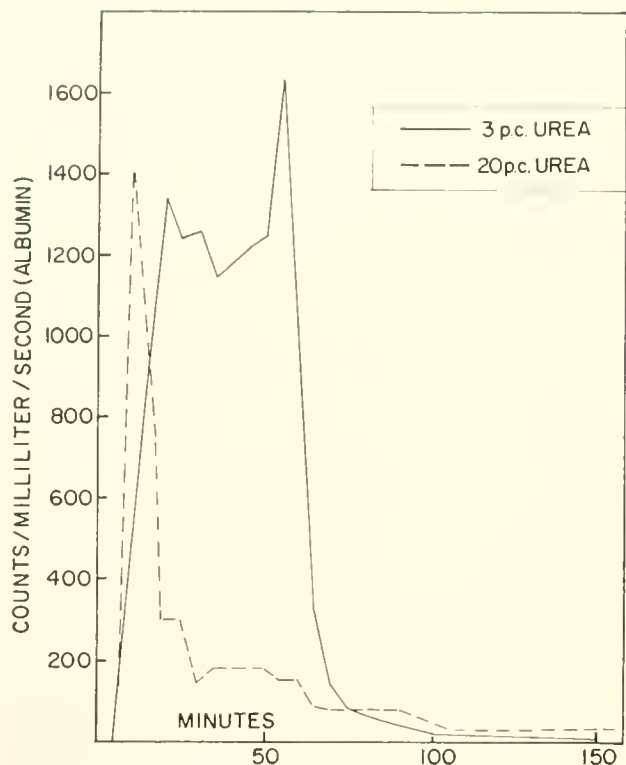


FIG. 6. Concentrations of urea in lymph. Same procedure as in experiment shown in fig. 5.

with the isolated lymph node preparation suggest that most of the 3 per cent or less not recovered from the thoracic duct goes into the blood stream via the popliteal node, and that there is little further loss in the other nodes through which the lymph passes on its way to the thoracic duct. We suspect that this is due to the fact that we are infusing under some pressure which is dissipated after the first node is passed. Nisimaru & Irisawa (156), in studying lymphatics of the frog's web, found that the permeability of injected lymphatic capillaries to particles of increasing sizes was directly related to increases in intraluminal pressure when applied via the lymph sac. Thus, patent blue dye escaped with 5 mm H₂O pressure, Congo red with 20 to 50 mm H₂O pressure.

We have tested a variety of substances of different molecular weights including dextran fractions, radioactive sodium (Na²²), urea, sodium thiocyanate, glucose, cellobiose, raffinose, and insulin. Briefly, we have found that all the macromolecules with molecular weight as large as or larger than 6000, the molecular weight of insulin, are retained almost quantitatively in the lymph ducts and are returned to the venous system by the thoracic duct. On the other hand, smaller molecules like sodium, urea, etc.

shuttle back and forth from lymph ducts and equilibrate with plasma very rapidly. Recently, we were fortunate in obtaining a dextran fraction of molecular weight of 2300. This substance appears to leave the lymphatic system as do the smaller substances. The limit of permeability thus seems to be somewhere between molecular weights of 2300 and 6000.

In these experiments, we always include radioactive albumin with the test substance and thus are able to assess any changes in permeability which may occur. In early experiments with urea, we infused high concentrations of urea (over 10%) in order to get a sufficiently high concentration for accurate analysis of our samples. Under these circumstances, there was a striking escape of albumin from the lymphatic system. Further experiments have shown that this phenomenon occurs only with concentrations of urea greater than 3 per cent (Fig. 6). Similar results showing increased leakage of albumin were obtained with the infusion of 25 ml of a solution containing 60 mg per cent sodium thiocyanate and 20 per cent radioactive albumin in saline. The mechanism of this apparently "toxic" effect of urea is being investigated as are the effects of high urea concentrations on blood capillary permeability.

Experiments with the isolated node preparation have given results which parallel those given above. As indicated, the small amount of albumin that finds its way to the plasma without going through the thoracic duct pathway evidently gets into plasma through capillaries of the node. The nature of this uptake has not been clarified. This preparation, although requiring patience and care in its use, should continue to be particularly useful in studies of uptake of other materials by nodes, and the functions of these nodes as part of the lymphatic circulation.

Much of the evidence relating to the absorption of substances by lymphatics has been concerned with absorption from the peritoneum. Here absorption occurs predominantly through those parts of the peritoneal surface of the diaphragm which overlie the lymphatic lacunes. To enter the lumen of a lymphatic lacune, materials must pass through a composite structure or "roof" consisting of *a*) a sheet of mesothelial cells, facing the peritoneal cavity and in continuity with the mesothelium of the rest of the peritoneum; *b*) a layer of connective tissue which forms a lattice of fibers; and *c*) an inner layer of endothelium in continuity with the endothelium in the walls and floor of the lacunae and ultimately with the endothelium of the efferent lymphatics.

The earliest and perhaps most tempting concept of

the mechanism by which macromolecules and particles entered lymphatics from the peritoneum was the postulation of openings in the endothelial walls. This concept was supported by the early work of von Recklinghausen (181a, 181b) and the presence or absence of "stigmata" and "stomata" have been debated for the last century. Cunningham (51a), in reviewing the subject in 1926, concluded, "In general, then, we may summarize the work which has been done on the mechanism involved in the absorption of particulate matter from the peritoneal cavity in the following way: The earlier work all tended to establish the concept of the presence of actual preformed physical openings between the peritoneal cavity and the diaphragmatic lymphatics. This idea was gradually eliminated and in its place the concept of potential physical openings between the walls was offered. In turn this hypothesis is being replaced by one which assumes that most, if not all, of the particulate material that is being absorbed from the peritoneal cavity passes directly through the cytoplasm of the mesothelial cells."

Lane Allen and his group have more recently revived the concept of potential physical openings. In experiments designed to test the upper limits of absorption, Allen (1b) injected intraperitoneally a variety of particles, yeast, mold, paraffin, and paraffin-asphalt spheres, and monitored diaphragmatic lymph for their recovery. He recovered spheres of mold of 10 μ , glass beads of 12.5 μ , and paraffin-asphalt spheres of up to 22.5 μ in diameter. He also recovered red blood cells in lymph at a level of up to 16 million per mm³. In later experiments, Allen & Weatherford (1c) injected polystyrene spheres with a range from chylomicron size up to 30 μ into the peritoneal cavities of mice, rats, and cats and recovered the particles from regional lymph nodes. The largest recovered spheres in the mouse were 16.8 μ in diameter, in the rat and cat, 24 μ . Allen (1b) presents his concept of diaphragmatic lymphatic absorption as follows: "As the diaphragm moves upward in expiration the lymphatic plexus expands and a relative negative pressure is established in the lymphatic lumen. At the same time the triple-layered membrane which separates the peritoneal cavity from lymphatic lumen is stretched. On either side of the fenestrations of the basement membrane the peritoneal mesothelium and lymphatic endothelium open, sometimes to form openings as great as 22.5 μ in diameter. Through these openings suspensions are 'sucked' into the lymphatic lumen. As the diaphragm contracts the tension on the lymphatic

wall is released, the openings close, and are no longer demonstrable by usual techniques, and compression of the plexus results in lymphatic flow."

The possible mechanisms of absorption of particles by the lymphatics of the diaphragm have been further clarified in a recent definitive study by French *et al.* (77a) using the light and electron microscopes. They point out that the mesothelial cells of the roofs differ from other cells at the peritoneal surface of the diaphragm in that they are more closely set, stain more darkly, and separate from each other more readily, particularly at the base of the intercellular junctions. The cells are supported by a lattice of coarse and fine fibers. In the meshes of this lattice, mesothelial and lymphatic endothelial cells are separated only by the basement membrane of the mesothelium which may be incomplete. The authors, using rabbits, injected India ink, thorium dioxide, and saccharated iron oxide intraperitoneally and found that the particles entered the intercellular spaces of the mesothelium and spread freely within the fibers of the fiber lattice. The particles appeared to pass through the mesothelium by a predominantly extracellular pathway and probably entered the lymphatic lumen through temporary channels formed by separation of endothelial cells at the intercellular junctions. These gaps formed by separation of mesothelial and endothelial cells also permit the passage of erythrocytes. The authors found that absorbed colloidal particles accumulated in the cytoplasm of mesothelial and lymphatic endothelial cells in the roofs, and their observations suggested that some of the absorbed material may be transported intracellularly through these two layers in cytoplasmic vesicles. In addition to uptake of particles by the endothelial cells in the roofs, cells in other sites in the diaphragm can also take up colloidal particles from the lumen of the lymphatic. In this respect, their results are similar to those of Odor (160a), who showed that particles of mercuric sulphide or Thorotrast were rapidly taken up from the peritoneal cavities of rats by mesothelial cells over the mesentery and diaphragm. On the other hand, Felix & Dalton (70a) found that melanin particles introduced intraperitoneally were actively ingested by free macrophages but not by mesothelial cells. These differences may be related to the difference in particle size or in the electron microscope preparations.

The evidence accumulated from recent studies thus suggests at least two possible pathways for the absorption of large particles (and erythrocytes) from the peritoneal cavity: 1) an extracellular pathway

consisting of gaps between mesothelial cells caused by pressure or, as suggested by Allen, by aspiration; 2) an intracellular pathway developed by infolding of the plasma membrane around particles and the subsequent pinching off of small pinocytic vesicles (13a). This vesicular mechanism may be concerned not only in transport from the exterior to the interior of the cell but also in transport through cells by a process termed cytopempsis (147a). The upper limit to the size of particles which can be absorbed through the extracellular route is probably determined by the size of the meshes in the connective tissue layer rather than by the potential openings between the mesothelial or endothelial cells. Smaller particles may travel through intercellular spaces in the roofs of the lacunes where the mesothelial cells separate from each other more readily than they do elsewhere. Evidence that small particles take an extracellular route through the lymphatic endothelium is perhaps not so convincing, but that particles can enter the interspace between lymphatic endothelial cells has been conclusively shown by Palay & Karlin (163a) in the central lacteal of an intestinal villus and by Casley-Smith & Florey (39a) in their study on lymphatics in ears of mice and guinea pigs, colons of rats, and diaphragms of mice. These authors suggest the possibility that lymphatic endothelial cells in general are less compactly joined than those in blood capillaries and may separate from each other more easily. The apparent absence of a continuous basement membrane to lymphatic endothelium, as discussed above, may possibly facilitate this separation of cells and be important in determining the permeability of lymphatic endothelium to macromolecules and particles traveling from without inward.

If we accept the fact that two possible pathways, intercellular and intracellular, are available for movement of substances through lymphatic membranes, their relative importance remains to be determined. How, too, are we to explain the striking difference between the ability of substances to enter and to leave lymphatic vessels? Cunningham reviewed the evidence available before 1926 and concluded that the main pathway of absorption is intracellular. Florey and his group, on the other hand, interpret their more recent results with the electron microscope as evidence of the possible greater importance of the intercellular pathway. They (77a) point out that there is no evidence that the greater permeability to colloidal particles shown by lymphatic endothelium when compared with blood capillary endothelium is explained by a greater frequency of cytoplasmic

vesicles. It is not too difficult, perhaps, to accept the point of view that the morphological basis of this relatively high permeability of lymphatic endothelium from without inward is related to cleavage at intercellular junctions and absence of a well-defined basement membrane. The available evidence from varied sources, although not always direct or definitive, is sufficient to suggest that mechanical factors, pressure and concentration gradients, elasticity of connective tissue, etc. (74a, 52a) may operate to move these substances from the interstitial space. Difficulty arises, however, in visualizing the same process as operating from within outward. Peters (171a) in 1935 appreciated this difficulty when he attempted to formulate a comprehensive theory of lymphatic absorption and raised the question as to how one could expect to hold water in a sieve by putting a valve at its mouth. Admittedly we still do not have sufficient information to provide an over-all sophisticated concept of permeability of lymphatic vessels. For the time being, it may therefore be wise to consider the following simple concept. We believe it to be consistent with the available evidence and to offer an explanation of the apparent one-way flow of materials into but not out of the lymphatics. Lacking evidence to the contrary, we may assume that the smallest terminal lymphatic capillaries are freely permeable to small and large molecules and particles moving in either direction through intercellular gaps. Compression of these vessels in any manner will force their contents in all directions. Some of the contents can, however, be forced centrally into larger vessels and ducts. The valves in these vessels will prevent backflow. Once the lymph reaches the larger vessels, it no longer loses its macromolecules and particles, since the walls of the larger vessels, as previously discussed, restrict molecules larger than molecular weight of approximately 2000 (at least in the dog).

This simple concept implies a relatively inept and inefficient system, a "leaky pump" system about which Peters complained. As Allen commented, however, a leaky pump will still pump, and as Drinker emphasized, the lymphatic system is, in the final analysis, a rather casual system. It does a reasonably good job under "normal" conditions. Its ineffectiveness becomes manifest chiefly under pathological situations. This aspect of the functions of the lymphatic system, its inadequacy in various pathological situations, will continue to merit careful study.

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The peripheral venous system

ROBERT S. ALEXANDER

*Department of Physiology, Albany Medical College,
Union University, Albany, New York*

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insight which anyone may gain into the function of the arterial system by the simple registration of arterial blood pressure. As a consequence, very few physiologists or students of physiology have had any personal opportunity to make observations, other than the experiments of Harvey, which could be interpreted with confidence as manifestations of venous function. A major effort of this presentation, therefore, will be to stress the technical problems of obtaining reliable information concerning venous function and to review the degree to which presently imperfect methods have yielded interpretations that are in substantial agreement. This will lead us to some positive convictions about the functional role of the venous system in spite of many unresolved problems of methodology.

ANATOMICAL CONSIDERATIONS

Structure

IF ONE WERE TO CONSULT TEXTBOOKS for information on venous physiology, the impression would be gained that knowledge of this subject has not progressed since the classical observations of William Harvey. The error of this misconception should have been laid to rest by the excellent review of Gollwitzer-Meier (36), in 1932 and the comprehensive monograph of Franklin (32) published in 1937. The bibliography of this monograph, containing well over 1000 references, is scarcely compatible with the ignorance of the subject which is often reported. It is our impression that a major deterrent to appreciation of our knowledge of venous function stems from a failure to develop valid techniques that can be applied to the venous system with ease and technical accuracy, comparable to the

In general structural pattern, veins are composed of the same elements as are the arteries, but with some important quantitative differences. Surrounding the endothelial lining of the lumen is a network of elastic and collagenous fibers which form a clearly defined intima only in the larger veins; in the smaller veins there is very poor differentiation of the intimal layer. Encircling these intimal fibers is the muscular media, which remains essentially a layer of spirally arranged smooth muscle fibers without any major contribution of elastic fibers. This lack of a heavy elastic investment of the media constitutes the major structural difference between veins and arteries. Externally, the vessel is surrounded by the meshwork of elastic and col-

lagenous fibers constituting the adventitia. The adventitial layer becomes the major component of the wall of larger veins.

Another important difference between arteries and veins is in the structural relationships adjacent to the capillary bed. Whereas the arterial channels possess significant muscle terminating in conspicuous pre-capillary muscular elements at the arteriole-capillary junction, minute venules are devoid of muscle. Converging capillaries become surrounded with a collagenous network to form small venules which may not acquire a continuous muscular media until diameters of the order of 0.5 mm are reached. It must be clearly recognized on a purely structural basis, therefore, that there is no mechanism at the venous end of the capillaries capable of throttling blood flow in the way that blood flow may be controlled at the arteriolar end (85).

In describing these general structural features of veins, reference is specifically being omitted to some of the important variations which are found in the adaptations of specific venous beds to local problems. By way of illustration, suffice it to say that in the long veins of the extremities there is the development of a significant component of longitudinally oriented muscle capable of counteracting the gravitational stresses to which these vessels are subjected, while within the cranium venules develop to considerable size without the appearance of any muscular elements (61).

Vasa Venarum

Crucial to an understanding of some aspects of venous function is a recognition of the role of the vasa venarum, which constitute the normal route through which both nutrients and vasoactive substances reach the vein wall. Older literature on this topic has been reviewed by Ramsey (76). There is a dense network of minute vessels in the adventitia of the larger blood vessels which is particularly conspicuous in veins. Although some techniques have failed to reveal a penetration of the capillary plexus into the media, adequate methods have succeeded in demonstrating a profuse capillary bed extending almost to the intima (67). In addition to the capillary plexus, there is clear evidence of an accessory duct system, presumably lymphatic in nature, which is distributed through the adventitia and media.

It must be emphasized, however, that the vasa venarum do not penetrate the intimal layer and drain through the local endothelium. Venous drainage from

the capillary plexus returns to venules running along the superficial layer of the adventitia, and eventually drains into either an entirely different vein or a remote site of the same vein. O'Neill has pointed out that this relationship assures that local obstruction in a venous segment will not block the flow in the vasa venarum, nor can local pockets of high intraluminal pressure induce backflow in the vasa venarum of the venous wall. A similar relationship exists in the arteries.

Functional confirmation of the anatomical relationships described above has been provided by O'Neill (67). Extensive damage to the intima followed stripping the tissues surrounding the vein so as to interrupt the vasa venarum, even though blood flow was maintained through the lumen of the vein. This indicates that oxygen and nutrients do not pass in significant amounts from the lumen into the surrounding tissue of the vein wall, and that the venous wall is clearly dependent upon the vasa venarum. Comparable evidence may be observed with drugs. Minimal response to vasoactive agents can be demonstrated when the drug flows through the lumen of the veins, while very effective vascular responses result when the drug is applied systemically or topically so that it may reach the media from the adventitial side.

This anatomical arrangement seriously handicaps the study of functional changes in the vasa venarum. In the case of arteries, the vascular wall is supplied not only by vessels penetrating from the adventitial side, but also by some vasa vasorum interna which penetrate the wall directly from the lumen. Smith (83, 84) has taken advantage of this relationship to use the amount of leakage, in response to internal pressure changes, from the surface of an excised arterial segment as a measure of vasa vasorum flow. A similar technique would not be applicable to veins. In the study of diseased veins, a further complication arises in that the anatomical pattern changes qualitatively as well as quantitatively. The early inflammatory phase of vascular disease stimulates a dense invasion of vascular elements into the wall of the vessel with the creation of venous channels that penetrate the intima directly into the lumen of the vessel, creating vasa venarum which have no counterpart in normal veins.

Innervation

Veins are copiously supplied with nerves which Thompson (86) demonstrated, in 1893, to be capable of producing constriction of the vein. Bayliss & Starling (8) confirmed the existence of neurogenic veno-

constrictor mechanisms and, on the basis of changes in arterial and venous pressure following spinal transection, inferred that the nervous system must be of importance in maintaining venous tone. Donegan (19) studied this innervation in greater detail and established that it was sympathetic in nature. As with other sympathetic pathways, localization is rather gross, with a given vein segment responding to stimulation from several adjacent spinal segments. There is now clear evidence of a tonic constrictor activity of this sympathetic innervation, since venous dilation occurs with sympathectomy (9, 54) or with sympatholytic drugs. This adrenergic sympathetic influence appears to be purely constrictor without any dilator component (62). Conversely, there appears to be no evidence of parasympathetic innervation of veins. Although pharmacological doses of cholinergic drugs may influence venous musculature, neither parasympathetic stimulation nor atropinization have any effect on venous tone (31). Even in such a highly specialized vascular function as penile erection, parasympathetic control appears to be restricted to the arterial side of the circulation, with the veins playing a purely passive role (47).

Venous Valves

A unique feature of the venous system is the presence of venous valves. The dramatic simplicity with which the nature of this valve action can be demonstrated in the veins on the dorsum of the hand remains one of the classical observations of physiology. Clinically, the role of the venous valves in the lower extremities have received particular attention. The superficial veins of the leg, lacking protection from surrounding muscle, are often subjected to prolonged hydrostatic loads. This excessive distension of the vessels may eventuate in valvular incompetence. The consequences of this valvular incompetence and its relation to venous varicosities and varicose ulcers has been analyzed extensively in the literature on peripheral vascular surgery. (See Burch, Chapter 36.)

This focusing of attention on the venous valves of the extremities has distorted an appreciation of the significance of valves in the venous system as a whole. For example, a widely prevalent notion is typified by the following statement from a leading textbook of histology (46): "Valves are especially abundant in the veins of the extremities and they are generally absent from the veins of the thorax and abdomen." In actual fact, valves or valve-like structures have been reported in most segments of the venous system,

although generalizations are difficult because of the marked species variation which has been reported (29). The distinguishing feature of the valves in the extremities is not their presence but the degree of competence which they exhibit; venous valves in areas not confronted with severe hydrostatic strains are usually more rudimentary and therefore less easily demonstrated.

An example of the latter type of valvular structure in abdominal veins is illustrated in figure 1 from a preparation made by Dr. Darrell Davis. This is a photograph of a plastic cast of venous vessels obtained by retrograde injection of a segment of dog intestine. Numerous valve impressions are clearly identifiable on this preparation. Just before each point of junction, most of the tributaries contain a valve. In every instance the injection mass terminates with a bilobed indentation which clearly represents a valve. Blood traversing this venous bed must pass through a series of valves before gaining access to the portal vein.

It should be appreciated that figure 1 also demonstrates a relative incompetency of these valves, in that the injection mass has readily passed beyond a number of the valves. Accordingly, in spite of the profusion of valves in this bed, it is reasonably easy to reverse the flow of blood in the intestine. If artery and vein of a loop of dog intestine are sectioned and a circuit re-established whereby the intestinal vein is connected to an arterial supply and the artery led out to a route of venous drainage, a substantial retrograde flow is observed for several minutes, eventually becoming reduced as massive edema develops from the abnormal capillary pressure relationships. Measurement of pressure gradients and flow demonstrates that retrograde flow encounters a resistance of three to ten times the vascular resistance to forward flow during



FIG. 1. Plastic cast of mesenteric veins of a dog demonstrating multiple valves. (Preparation made by Dr. Darrell Davis.)

the early phase of the reversal. While a good part of this resistance is undoubtedly attributable to the valves, the situation contrasts with that observed in healthy veins in the extremities where valves present infinite resistance to retrograde flow until very high pressures are reached.

The functional contribution of venous valves should be clearly defined. In the idealized circulatory scheme with continuous venous flow, the valves must necessarily remain open and hence make no functional contribution. With intermittency of flow, due, for example, to intermittency of flow in the peripheral bed, the valves would tend to close during the intervals of flow cessation. Nevertheless, we must reject the view that this "breaking up" of the venous column into segments relieves the dependent parts from the hydrostatic load of a continuous fluid column. The hydrostatic gradient is inherent in the hydraulics of the system; energetically the valves cannot contribute to the need for adequate pressure energy to overcome the hydrostatic barrier between dependent parts and the heart. In the system as a whole, intermittent flow must preserve the same mean pressure gradient as is required of continuous flow.

Valves make their functional contribution by translating extramurally applied forces into flow energy. When an external force compresses a fluid-filled vessel, local intramural pressure will rise and tend to drive the blood in both directions from the point of compression. The actual flow which will occur in the two possible directions will be a function of the pressure gradients and resistances in the alternate directions. The resistance to retrograde flow toward the capillary bed is far higher than the resistance to forward flow toward the heart, and the pressure gradient, which normally favors central return, would very strongly favor central flow the moment the retrograde flow combined with continuing capillary drainage to build up peripheral venous pressure. Thus it should be appreciated that a "milking" action of intermittent venous compression will effectively propel blood toward the heart even in the complete absence of valves. Valves, however, can greatly increase the efficiency of this process by producing an almost immediate rise of retrograde resistance to infinity.

The importance of this process is most clearly demonstrated by the dramatic relief from orthostatic hypotension which is produced by movements of the legs and their associated compressing forces on the leg veins. Walking movements are so effective in propelling flow up the venous channels that they can

restore adequate venous return to the heart even when vasomotor tone has been completely abolished by sympatholytic drugs (71). Direct measurements have demonstrated that the sequential compression of venous segments during walking milks blood up the legs efficiently enough to reduce the pressure in the uncompressed veins of the ankle to less than one quarter of the hydrostatic gradient from the ankle to the heart (74). There is no question that such extravascular forces constitute a significant "booster pump" (49) for maintaining the circulation. The idea championed by Henderson (48), that muscular activity acting in conjunction with the venous valves was the primary "venopressor" mechanism, should therefore not be dismissed lightly, even though this mechanism does not appear to play quite such a comprehensive role in maintaining venous return as Henderson claimed (90).

Venous Capacity

Because of the relatively large caliber of veins, and also the conspicuous venous sinusoids which occur in some organs, it is commonly supposed that the capacitative function of the vascular bed resides dominantly in the venous system. The full functional significance of this concept will be developed in the next chapter. Our concern at the moment is confined to examining the evidence underlying this basic assumption.

Widely quoted data in support of this venous reservoir concept are those published by Green (37) calculated from an analysis of the intestinal vascular bed of the dog reported by Mall. These data picture some 70 per cent of the vascular capacity to reside in the venous system with 62 per cent in veins greater than 1 mm in diameter. Landis & Hortenstine (58) carried out a very similar calculation based upon the intestinal data of Schleiser, which yielded a value of 75 per cent of the vascular volume within the venous system, 50 per cent of the total being found in veins greater than 1 mm in diameter. The Landis calculation did not include the venae cavae, inclusion of which would have increased the percentage of volume in the large veins.

It is distressing, however, when one realizes how little direct evidence there is to support these estimates. By measuring the mean transit time for dye passage between the femoral vein and the right atrium, Milnor & Bertrand (65) were able to calculate a volume between these two sites which averaged 18 per cent of the total blood volume. Since the inferior vena caval system is a notoriously poor mixing

chamber, one would expect the true volume to exceed that calculated by this method. This study therefore represents some substantial support for the idea that large veins represent a significant contribution to the total vascular capacity. On the other hand, Knisely and associates (57) have challenged the conventional point of view with some data obtained from plastic injections of whole rats. Using a plastic free of particulate matter which flowed freely through the circulation when initially injected, they obtained casts of the entire vascular bed. When these casts were fragmented, and the fragments sorted according to caliber, over 80 per cent of the plastic was found to be contained in vessels with a diameter of less than $200\ \mu$ and only 12 per cent in vessels larger than $700\ \mu$. This study suffers from the fact that veins are collapsible, and it is not at all clear that their method would have preserved a normal degree of filling of the venous system. Nevertheless, such an extreme discrepancy between the relative contribution of large vessels and small vessels to total vascular capacity clearly challenges the point of view that is usually held. The burden of proof has been returned to the proponents of the venous reservoir concept to offer some more substantial documentation of their hypothesis.

Apart from the question of total capacity, however, there is much better support for the thesis that the venous division, together with the lesser circulation, is the most variable capacity of the vascular bed. One very simple observation leading to such an inference is the minimal change in pressure produced by an injection into the venous system as compared to the pressure change produced by an injection of an equal volume at the same rate into the arterial system. More direct evidence on this point was presented by Greenfield & Paterson (39), who compared volume changes in the forearm produced by venous obstruction to the volume changes produced by a negative pressure applied to the whole arm. In the former instance, the increase in transmural vascular pressure would be essentially confined to the venous side; in the suction experiment, the transmural pressure of all vessels should be increased equally. Yet venous occlusion provided 85 per cent of the volume increase observed when suction was applied to the whole arm. A similar experiment was reported by Capps (16). Such data, together with venous distensibility characteristics to be discussed later, justify reasonable confidence in the hypothesis that the venous system plays an important role in contributing a reservoir of variable capacity to the vascular system.

PHYSIOLOGICAL CHARACTERISTICS OF VEINS

Principles of Venous Hemodynamics

The most frequent measurement made of the venous system is the venous pressure. For the purposes of our interests however, venous pressure is of relatively little meaning. As competently reviewed by Landis & Hortenstine (58), venous pressure can have profound influence on capillary dynamics and the transudation of fluid across the capillary endothelium. Central venous pressure plays a key role in cardiac filling and the control of cardiac output. For reasons that will be developed shortly, however, venous pressures tell very little about the venous system itself. Indeed, it can be fairly stated that venous pressure measurements in themselves are just as unimportant to the physiologist interested in the venous system as they are important to the physiologist interested in the arterial system.

Before specifically considering the principles of hemodynamics underlying this statement, a word of emphasis should be given in reference to the implication of the studies of Pappenheimer (69, 70) on the capillary bed. He has lucidly argued that, under steady-state conditions, the mean capillary pressure must be in equilibrium with the effective osmotic pressure of the plasma proteins, excluding lymph flow which at best is a small fraction of total blood flow. Since central venous pressure shows relatively small variations under most conditions, this indicates a relatively constant pressure gradient from capillaries to the central veins. Furthermore, large changes in blood flow may occur without significant alterations in either plasma protein concentration or central venous pressure, yielding the apparent paradox of blood flow that varies widely in spite of a fixed pressure gradient. A corollary to this is that the venous smooth musculature cannot effectively control blood flow by imposing a variable resistance in the venous portion of the circulation. The role of the venous musculature must therefore be confined to producing capacity changes in the system. These capacity changes can indirectly influence blood flow only insofar as more effective venous return increases cardiac output, or higher mean circulatory pressures increase capillary transudation.

If some of the preceding statements appear to be in conflict with irrefutable principles of fluid dynamics, the reader must be reminded that the venous system is a collapsible system and is therefore not governed by the usual principles of fluid dynamics in

cylindrical tubes. The phenomenon of venous collapse was inherent in the classical observations of Harvey. It has remained a commonplace observation in the use of the height above the heart at which superficial veins collapse as a clinical estimate of central venous pressure. Yet the hemodynamic significance of venous collapse has been all too rarely appreciated.

First, it is important to note that "collapse" of veins is not an all-or-none characteristic. Complete collapse of the vein with obliteration of its lumen represents an obstruction to blood flow which can only exist on a transient basis. The collapse phenomenon relates to the fact that the vein wall is not structurally self-supporting. Energy is required to push the vein walls out into a cylindrical configuration. Any time that the intraluminal pressure becomes equal to or less than the extravascular pressure, the venous walls will tend to approximate each other in an ellipsoidal cross section (73).

This is best visualized by examining veins above heart level. Hydrostatic forces will act to drain blood from these veins and create a negative intraluminal pressure. In addition, finite tissue pressures always produce some degree of positive extravascular compression. In the absence of blood flow, such a vessel would remain completely collapsed. To preserve flow in such a segment, intraluminal pressure must be raised until it slightly exceeds the extravascular pressure so as to open the collapsed vein. Intraluminal pressure must further be elevated enough above extravascular pressure to provide the necessary pressure head to produce forward flow against the resistance it confronts. However, since a slightly positive transmural pressure will widen the collapsed lumen and produce a marked fall in resistance, very little pressure gradient is required to produce flow. Therefore, the pressure measured in veins that are above heart level will be essentially the same as the extravascular tissue pressure, as originally emphasized by Holt (51, 52, 80). It follows that such pressures have no hemodynamic significance in the usual sense of gradients along the vascular circuit, and they are in no way specifically related to constriction or dilation of the veins.

A more rigorous statement of this relationship has been clearly set forth in the exposition by Brecher (11). The classical formulation of the Poiseuille law for cylindrical tubes:

$$\text{resistance} \propto \text{radius}^4$$

must be modified for collapsible tubes to the more

complex expression:

$$R \propto \frac{2a^3b^3}{a^2 + b^2}$$

in which R is resistance and a and b are the major and minor axes of the ellipse. It should be noted that in a cylinder where $a = b$, the second expression reduces to the first. As an operational tool, this formulation of resistance relationships is rarely of practical value to the physiologist because the desired dimensions are not accessible. Nevertheless, from a theoretical standpoint it defines the fact that resistance to flow will increase markedly as the vessel progressively collapses to a flattened ellipse.

The full import of this collapsibility resides in the consequences it has upon the significant variables determining blood flow. In a system of cylindrical tubes, as represented by the arterial system, pressure is normally maintained at homeostatic levels in the arterial reservoir and, for any given vascular bed, blood flow is controlled by resistance changes through the activity of the vascular smooth muscle in the arterial supply to that bed. To emphasize this point, one might consider the pressure as essentially constant (P_a) under a given situation and the significant variables of flow (\dot{Q}) and resistance (R_a) expressed as:

$$\dot{Q} = \frac{1}{R_a} \times P_a$$

In contrast, in any local venous bed, the flow is obligate since in a steady state the veins must transport the volume of blood delivered by arterial inflow. Flow may therefore be considered constant and in any venous segment resistance is controlled by the local pressure (P_v) which, as outlined above, must represent a small increment over the extravascular pressure:

$$R_v = \frac{1}{P_v} \times \dot{Q}$$

Stated descriptively, in the venous system operating under a state of partial collapse, local venous pressure determines the cross section of the ellipse and thereby adjusts resistance to accommodate the volume of flow presented to the system.

Extending this analysis further, in the arterial system an increase in the reference pressure (P_a) will immediately lead to an equivalent increase in the flow (neglecting factors of vessel elasticity and autoregulation). In the venous system, an increase in the reference flow (\dot{Q}) will tend to increase pressures slightly along the venous route. This will widen the

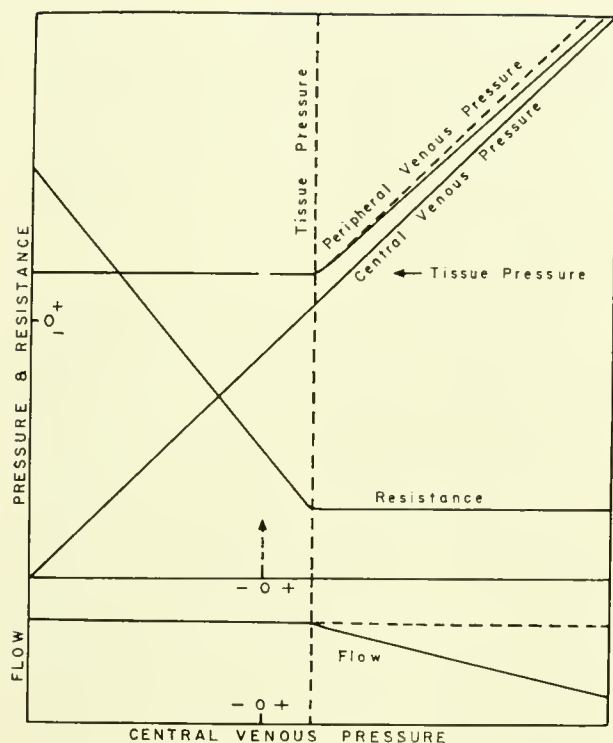


FIG. 2. Hemodynamic relationships in the venous bed, adapted from Holt (51) and Brecher (10). Solid lines indicate relationships without compensation; dashed lines indicate relationships with compensation in arterial inflow resistance. "O" pressure refers to the hydrostatic level of the peripheral vein.

ellipse and lower resistance so as to support an increased flow without change in the total pressure gradient from capillaries to heart.

The key relationships in this pattern of venous hemodynamics are illustrated in figure 2. For veins above heart level, the hydrostatic column of blood descending toward the heart creates a potentially subatmospheric intraluminal pressure tending to suck the walls of the vein in to cause collapse. Typically, this phenomenon will be most manifest at the point just before the venous channel enters the thoracic cavity, since in this region the negative intrathoracic pressure combines with the hydrostatic forces to aspirate blood from the veins. At the left of figure 2, therefore, central venous pressure is indicated as below atmospheric pressure; yet peripheral venous pressure is maintained at a definite positive value. Since under these conditions there is a significant pressure gradient, an appreciable resistance exists between the peripheral and the central veins. This resistance is created by the state of partial collapse near the central end of the channel. As the central

venous pressure rises toward atmospheric pressure, the aspiration effect causing collapse becomes progressively less, so that the resistance to flow progressively lowers. Peripheral pressure, however, remains unchanged. As the central venous pressure rises above atmospheric pressure, there continues to be an interval when the intravascular pressure remains below the extravascular pressure because of the existence of a positive tissue pressure in the area surrounding the veins.

As the central venous pressure reaches the value of the extravascular tissue pressure, a dramatic alteration occurs. The intraluminal pressure will now be sufficient to prevent collapse of the vein. As a consequence, the venous channel is distended and the more typical Poiseuille relationship pertains. Neglecting the minor influence of elastic distension of the veins, resistance between the peripheral and central veins remains constant at a relatively low value, and correspondingly a relatively constant small pressure difference exists between the peripheral and the central veins. Peripheral venous pressure will therefore rise almost parallel with central venous pressure.

It is to be emphasized that at all central pressures below the level of tissue pressure, the peripheral venous pressure remains at essentially the same level as the tissue pressure. Assuming there are no changes in arterial pressure or resistance factors, a constant peripheral venous pressure dictates a constant capillary blood flow. It is to be noted, therefore, that flow remains constant in spite of the significant changes in pressure gradient and resistance along the venous route. Once the central venous pressure rises above the tissue pressure, venous congestion occurs with a rise in peripheral venous pressure and a corresponding reduction in the arteriovenous pressure gradient. This will have some influence in reducing flow through the system unless compensated by other changes. In actual fact, a large rise in peripheral venous pressure reduces peripheral blood flow so that vasodilator metabolites accumulate in the tissues. The resulting compensatory dilation of the arterial inflow channels will counteract the elevation of peripheral venous pressure and maintain constant flow, as illustrated in the dashed lines of figure 2.

Any factors leading to a change in the extravascular tissue pressure will produce an equivalent change in the peripheral venous pressure, a corresponding alteration in resistance, and a shift of the point of inflection of the curves. Flow, however, will remain unchanged.

Students of the venous system must wrestle with

this concept until they come to recognize its profound implications. While the application of Poiseuille's law to collapsible tubes requires only minor modifications in arithmetic, the degree of determinacy of the respective variables is radically different. For example, there is a vast body of older literature which demonstrates that venous pressure is not altered by a host of physiological factors known to alter the regulation of the cardiovascular system. The conclusion of these authors, that the venous system therefore played no part in cardiovascular regulation, may be a significant reason why most textbooks are devoid of positive statements in regard to venomotor mechanisms. What these experiments actually proved was that the various experimental maneuvers had no effect on the extravascular tissue pressure which is the major determinant of venous pressure; such measurements are completely meaningless in reference to venous tone.

It would be a serious error, moreover, to regard the collapsibility of veins as a structural defect in the system which serves no better purpose than to complicate the understanding of venous hemodynamics. Since the venous system operates in the same pressure ranges as the gravitational forces and tissue pressures to which it is exposed, drastic disturbances would result if veins were rigid tubes. Consider, for example, an individual turning a handspring. If veins were rigid, there would be drastic surges in venous blood flow and chaotic alterations in venous return to the heart. More conventional running and jumping movements would seriously tax the homeostatic adjustment of a low pressure system of cylindrical tubes. The collapse mechanism serves to check such hydrostatic shifts of venous blood. As soon as pressure in the veins becomes reduced to tissue pressure levels, collapse occurs to throttle flow and maintain the peripheral bed at more nearly normal functional levels.

Duomarco and associates (22-24) have extended this concept of venous hemodynamics to claim that the design of a collapsible venous system guarantees that extravascular factors capable of altering pressure relationships can have no influence on venous flow. Duomarco's enthusiasm for the teleological magnificence of such a scheme apparently exceeds the actual facts. It must be appreciated that, with normal blood volume, a significant fraction of the venous bed is distended so that it does behave as a system of cylindrical tubes. This will hold for most of the extrathoracic veins which are below heart level and which are not in regions subjected to significant extravascular compression. Furthermore, the work

of Brecher (10) has established that phasic pressure changes are capable of producing phasic changes in flow during the intervals when geometric adjustments in the degree of collapse are taking place. Such phasic pressure changes are conspicuous in intra-thoracic and intra-abdominal veins in association with respiration, and also seem to be a characteristic manifestation of venous vasomotion in the small peripheral veins (44).

An additional word of caution should be appended to emphasize that there are some important exceptions to generalizations as to the collapsibility of veins. This is particularly true of venous structures that are bound by connective tissue to rigid skeletal elements which prevent their collapse, such as the sinuses of the dura mater and the vertebral venous sinuses. In these vessels, gravitational or respiratory forces may lower the intraluminal pressure to values significantly below the pressure existing on the outside of the vessel. A clinical consequence is the danger of air aspiration into the vascular system if these vessels are opened to the atmosphere during surgical procedures or by accidental trauma. A similar problem exists to a lesser degree at the point where veins enter the chest. The thyroid surgeon is well aware that veins near the base of the neck have sufficient connective tissue attachments so that traction may pull open an incised vein that has not been securely ligated, and acroembolism result when inspiratory pressure changes lower the central venous pressure below atmospheric pressure.

To qualify generalizations about venous collapse, however, should not obscure the importance of this phenomenon in venous function as a whole. Any approach to the venous circulation which neglects the collapsibility of veins will lead to serious distortions of the hemodynamic factors which control the flow of venous blood.

Venous Distensibility

In view of the collapsible nature of veins, a vein segment will empty freely from cut ends, the vessel will flatten and all blood will leave the lumen except for a minute amount retained within the folds on opposite sides of the vessel. If fluid is now added to this collapsed vessel, two theoretically distinct processes will occur. The first phase will be "filling," during which the geometry of the vessel wall is restored to the cylindrical shape without increasing in circumference. The succeeding phase will repre-

sent elastic distension of the vein segment through increase in its circumference and length.

The inference sometimes encountered, however, that the vein remains at "zero" pressure until it is "filled" is quite unrealistic. Some finite pressure is required to restore the wall to its cylindrical shape. For veins in situ, filling the vein must also overcome tissue pressure, and local tissue pressure will itself be augmented by the swelling of the vein. Finally, as fluid starts to fill the vein, hydrostatic pressures will be created unless the vein is perfectly horizontal. Consequently, if one records intraluminal pressure accurately while fluid is progressively added to an empty vein in vivo, pressure starts to rise almost immediately and does not show any recognizable inflection when the vein is "filled" (fig. 3).

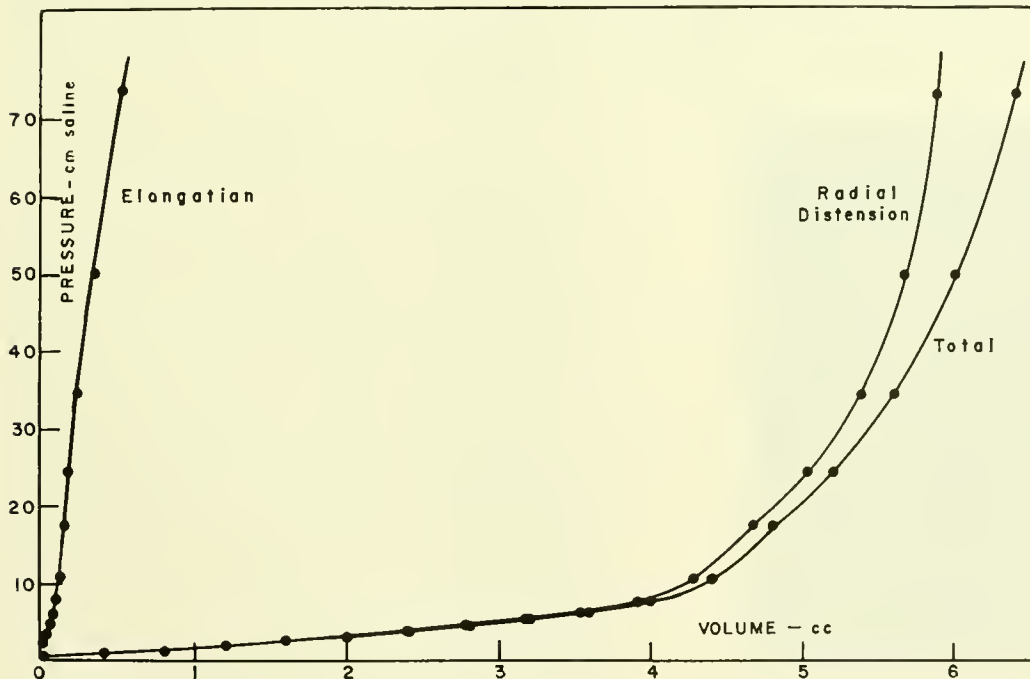
The pressure-volume curves obtained from venous segments, or the tension-length curves obtained from strips or rings, are most commonly described as curvilinear with considerable convexity toward the length or volume axis. Clark (17) was the first to recognize that these two types of measurement must be related by the Laplacian relationship whereby in a cylindrical tube, wall tension (T) increases as a

function of pressure (P) and radius (R):

$$T = P \times R$$

It follows that at small radii, relatively less wall tension is created by a given pressure increment than at large radii. The pressure-volume curve shows correspondingly less curvature than the tension-length curve.

Figure 3 illustrates the volume change due to radial distension as contrasted with the volume increase due to elongation. It is apparent that most of the volume increment results from radial distension within the physiological range of venous pressures. It is only above pressures of 30 to 40 cm H₂O that radial distension becomes restricted to the relatively low degree of distensibility which is characteristic of longitudinal distension. A further important characteristic of the longitudinal distension of veins, that is not shown by such data, is the spiral twist which veins exhibit when they are subject to sufficient pressure to produce significant longitudinal stretch. Presumably because of the spiral structures within the vein wall, there is a definite rotation of one end of the vein in respect to the other end as the vein lengthens. Teleologically,



it appears reasonable to suggest that this spiral twist of a distended vein may be of importance in relieving kinking of the veins when the tissue is mechanically distorted.

Quite a different curve of vascular distensibility was presented by MacWilliam (60) as shown in figure 4. He took the precaution to collect fresh tissues and observe their behavior carefully during the postmortem period. Shortly after a segment of living vessel was excised, it developed marked spasm. This spasm persisted for many hours if the tissue was kept cool. In this contracted condition a stretch curve, such as that shown in the lower half of the figure, was observed. When the state of contraction was eliminated by warming the vessel, a more conventional stretch curve was obtained as shown in the upper portion of the figure. The marked sigmoid curve observed originally has now been replaced by a simple bow convex to the length axis. MacWilliam interpreted the lower curve as a manifestation of the resistance to stretch of the smooth muscle, which gradually gave way as tension increased until eventually stretch was restricted by the elastic and fibrous tissue of the vessel wall. The upper curve lacked this muscle component, and therefore revealed the simpler manifestation of elastic tissue distension. This change in the distensibility pattern was quite characteristic of arteries; it was not so evident in the veins studied by MacWilliam.



FIG. 4. Stepwise loading of a ring of artery which in the lower section was in a contracted state from preservation in the cold. In the upper tracing the identical loading sequence was repeated after the vessel had been dilated by warming. [From MacWilliam (60).]

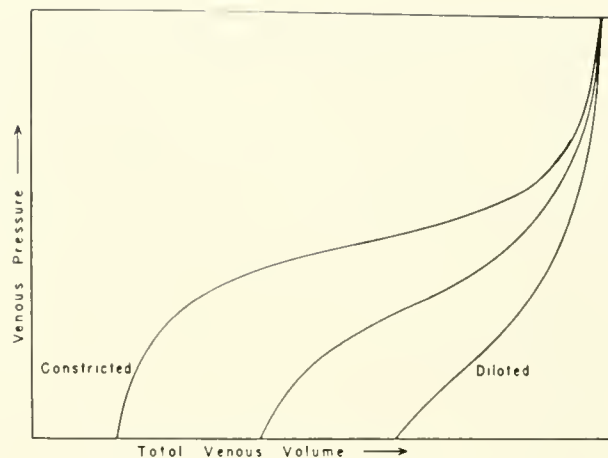


FIG. 5. Distensibility patterns recorded from veins in vivo (4).

A majority of investigators have considered this spasm of the excised vessel as a postmortem artifact, and many describe techniques employed to remove this state of spasm in the tissue before carrying out studies of its elastic behavior. The potential significance of this observation of MacWilliam therefore lay dormant for many years, until Capps (16) observed the same type of curves in plethysmographic recordings obtained from the human arm. The sigmoid type of distensibility curve was associated with constricted veins, and the smooth bow was associated with dilated veins.

More recently the significance of this distensibility pattern of constricted vessels and of dilated vessels has been analyzed by the author (2-4, 78). There is now ample evidence that these distensibility patterns are exhibited by living veins in vivo (fig. 5) and, as will be discussed later, their analysis can serve as a useful index to the state of contraction of the veins.

Another feature of vascular distensibility, which has been recognized since the time of Roy (79), is the marked time dependency in elastic behavior (1). This has been variously identified as "elastic after-action," "elastic hysteresis," "delayed compliance," or probably more properly by the physical phenomena of "stress relaxation," in which pressure dissipates following sudden distension to a constant volume, and "creep," in which volume slowly increases after sudden distension by a constant pressure. With a continuous cycle of injection and withdrawal of fluid, this characteristic manifests itself as a wide loop of disparity between the pressure-volume relationships observed on injection and the pressure-volume relationships found on withdrawal (figs. 6 and 7). To a degree, the width of this loop demonstrates time dependency, in that it tends to become

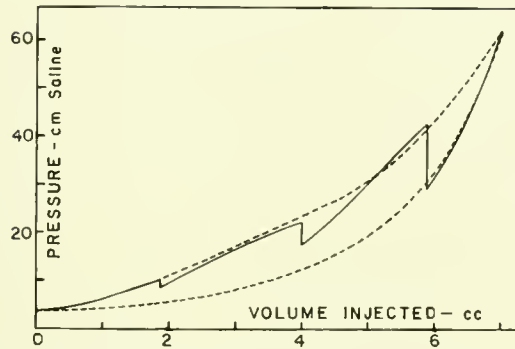


FIG. 6. Continuous injection (upper dashed line) and withdrawal (lower dashed line) of blood into mesenteric veins of a dog at the rate of $37.5 \text{ cm}^3/\text{min}$, compared with an injection performed at the same rate but interrupted at three points for intervals of 10 sec. Note that the stress relaxation, demonstrated by the loop in the continuous curve, is significantly greater as the higher pressures are reached in the interrupted curve (38).

narrower at very fast and very slow rates of injection, being widest when the rate of injection and withdrawal permits the greatest degree of stress relaxation to occur between the injection phase and the withdrawal phase. In addition to this simple visco-elastic type of behavior, moreover, veins also exhibit plastic properties, in that the stress relaxation is minimal at very low pressures, and becomes disproportionately exaggerated at higher pressures, as indicated in figure 6. It appears that certain "yield pressures" are required to produce the transformation which gives rise to the stress relaxation.

The complex problem of the exact basis for these properties of blood vessels (78) is beyond our scope here, but it should be appreciated that these characteristics have two implications of importance in evaluating distensibility determinations. First, pressure-volume data obtained from veins are strongly influenced by the exact conditions of venous distension, and data are never rigorously comparable unless identical rates and magnitudes of distension are used. Unfortunately this requirement has often been overlooked, and a large bulk of published data must be questioned because of failure to impose exactly defined and standardized procedures for obtaining distensibility determinations.

A second important facet to this problem is the effect of a repeated stretch. As is to be expected of a tissue showing a significant stress relaxation, a second stretch curve differs greatly from an initial stretch. This characteristic is most prominent in the constricted vein, in which the sigmoid pattern of distensibility characteristic of an initial stretch is obliterated in succeeding stretches (5). Studies have

shown that 20 to 30 min are required for a complete restoration of the initial distensibility pattern following an initial stretch of the tissue. Related to this is the fact that the distensibility pattern observed on release of stretch of a constricted vessel is identical to the pattern observed with the release of stretch of a dilated vessel (fig. 7). Stretch of the tissue appears to "pull out" the muscle so that it no longer contributes to the distensibility characteristics of the tissue until considerable time has elapsed for this muscular influence to become restored. This dictates that not only must precise distensibility data be gathered with rigorously defined rates of stretch, but also the intervals between stretches must be rigidly controlled.

A further problem should be mentioned to which there is at present no satisfactory answer. Many have argued that distensibility data have no absolute meaning until they are converted into terms of a quantitative modulus of elasticity which relates the tension-length or pressure-volume increments to the initial length or volume parameters of the tissue. There are certain practical difficulties which interfere with accomplishing this objective. With *in vivo* measurements, accurate estimates of initial dimensions are extremely difficult to obtain even when pressure and volume increments are readily measured. Furthermore, inherent to the calculation of an elasticity modulus is the assumption of homogeneity of the tissue, and some investigators have questioned whether a meaningful modulus can be calculated from tissue

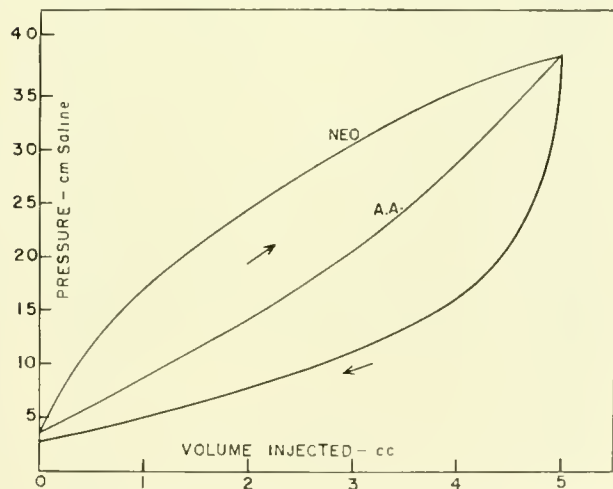


FIG. 7. Injection and withdrawal of blood at the rate of $50 \text{ cm}^3/\text{min}$ into mesenteric veins of a dog constricted by neo-synephrine (NEO) and subsequently dilated by adenylic acid (A.A.). The injection curves demonstrate the characteristic convexity and concavity patterns portrayed in fig. 5, but the withdrawal curves were perfectly superimposed.

dimensions which include many components in addition to those controlling the elasticity of the structure. As a consequence, most of the data in the literature are presented as pressure-volume increments of a system, the total volume of which remains undefined.

A significant point in this connection relates to the interpretation of the sigmoid distensibility pattern of the constricted vein (fig. 5). If we accept the interpretation given that stretch acts to "pull out" the muscle so that distensibility is eventually restricted by the elastic and fibrous tissue, it follows that at extreme degrees of stretch both constricted and dilated tissues should possess the same length at the same tension. The record in figure 4 accords with this as a first approximation, although actual measurements reveal a minor discrepancy in the recorded lengths. *In vivo* measurements, by direct injection (2) and by indirect plethysmographic studies (39), also suggest that with maximum distension the volumes of constricted and dilated veins converge. Burton (15), however, has challenged this interpretation, and offered evidence that constricted vessels retain a smaller caliber than dilated vessels regardless of how much they are stretched. Recent studies on isolated tissues, the dimensions of which can be accurately recorded, have thrown additional light on this problem (77). There appears to be no fixed correlation between the unstretched length of a tissue and the pattern of its distensibility curve. Although repeated stretch of a constricted tissue can eliminate the sigmoid distensibility pattern and yield a convex curve indistinguishable from that of a dilated tissue, this stretch does not erase the shorter unstretched length of the constricted tissue. In other words, the "pulling out" of the muscle by stretching a constricted tissue does not transform it into a dilated tissue. An ultimate resolution of the nature of these changes must await a fundamental understanding of tissue elasticity, very probably extending to the molecular level (78). Until that understanding is at hand, we must be cautious not to oversimplify the distensibility characteristics of veins.

Nature of Venous Constriction

Most references to venous constriction visualize a uniform increase in tonic activity of the muscle so as to reduce the caliber of the vessel, without further definition of the process or processes involved. There is evidence, however, that in addition to increases in venous tone there are more extreme and more sus-

tained forms of venous constriction which justify the designation of "venospasms." The latter may be localized or may involve more extensive segments of the venous bed.

The local spasm which frequently is induced by the trauma of venipuncture is a commonplace observation to both the experimentalist and the clinician. Since this response cannot be abolished by denervation, it must include a significant local mechanism in its genesis. Inversely related to this traumatic venous spasm may be the localized dilation which can be evoked by tapping a vein (33). There are also occasional reports of localized rings of constriction in a venous bed under conditions where there appears to have been uniform stimulation of the bed. Such irregular segments of constriction are shown in figure 8, which illustrates intestinal veins following the intra-arterial administration of levarterenol. In extreme cases, this pattern of reactivity may distort the vein so that it resembles a string of sausages, with rings of constriction separating distended segments.

There are two plausible lines of explanation for this type of segmental venospasm. One could relate to anatomical or functional differentiation of different regions of the vein wall in which certain segments are more sensitive to stimulation or more powerful in the magnitude of response that they can develop. Another possible explanation relates to the Laplacian phenomenon discussed earlier (17). The moment one area of vein reduces its caliber slightly more than an adjacent area, its mechanical ability to compress the lumen increases, even though the tangential tension

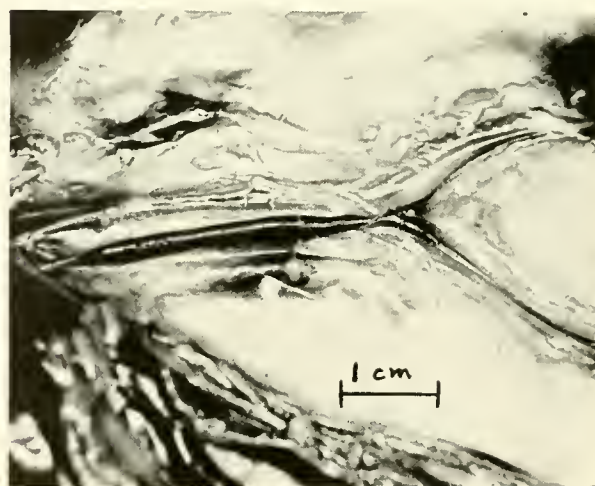


FIG. 8. Segment of dog mesentery following the intra-arterial injection of levarterenol, demonstrating the irregular distribution of constriction sometimes exhibited by veins.

in the wall remains the same. Much as in the classical soap bubble or balloon experiments, the smaller element will force its contents into the larger element. Although more information is needed to clarify this phenomenon, it appears worthy of mention because of its possible relationship to certain aspects of venous varicosities.

The phenomenon of more generalized venospasm still remains largely unsolved. An important characteristic is that this type of venospasm involves a significant neurogenic spread which influences both arterial and venous elements so as to throttle blood flow through the entire bed. In experimental venous thrombosis, for example, the reduction in blood flow to an extremity far exceeds anything attributable to the local mechanical block, apparently due to reflex constriction involving all vascular elements of the limb (66). A suggestion as to the factors responsible for the maintenance of venospasm under these conditions is found in the observations of Donegan (19). In the presence of good blood flow and well-filled veins, nerve stimulation evoked a brief phasic constriction of veins which resembled the typical response of smooth muscle to nerve stimulation. When a vein was poorly filled, on the other hand, little detectable response was observed unless intense stimulation was given, whereupon the vein constricted strongly and remained constricted for a period of 6 to 12 min. It is therefore evident that venous distension has an influence on the ability of the venous musculature to contract maximally, which is quite compatible with the influence of venoconstriction on venous distensibility, as previously discussed. It leads us to the conclusion that venospasm is a phenomenon produced when dynamic conditions are such as to displace the vein over to the bottom of the sigmoid distensibility curve (fig. 5). It is still far from clear, nevertheless, as to just what types of conditions of stimulation can evoke such a venospasm.

ASSESSMENT OF VENOMOTOR ACTIVITY

In Vitro Studies

The most direct method for studying venous smooth musculature is to measure the reactivity of rings of venous tissue in vitro. Rings, circumferential strips, or spirally cut strips (59) are most suitable for such studies; longitudinal preparations exhibit minimal change. It was with such venous rings that Gunn & Chavasse (40) first demonstrated clearly that veins contract strongly in the presence of adrenergic drugs. This adrenergic response has remained somewhat

of a reference standard for comparing other agents, and for evaluating the effectiveness of other techniques for measuring venous tone. The action of many other agents has been examined in isolated preparations, so that there has developed an appreciable literature on the pharmacology of veins (28, 30, 61). Although the basic importance of these in vitro studies must be recognized, such techniques give us limited insight into the physiological responses of veins in vivo.

Direct Observation

The simplest method for detecting activity of the muscular elements of a vein in vivo is to observe changes in the caliber of the vein. Many such observations have been reported and much valid information has been deduced from such observations. As a general approach to the problem, however, this technique cannot be accepted as reliable. The observer can only detect changes in the volume of blood within the vessel. This change in blood volume may be caused by *a*) changes in flow through the peripheral vascular bed, *b*) alterations in the pressure and/or resistance to flow in more central portions of the venous channels, *c*) changes in the extravascular tissue pressure, or finally *d*) changes in the venomotor tone in the vessel under observation. Unless the first three factors can be confidently excluded, it is hazardous to infer that the last factor is the crucial variable.

It is rare that simple observation of veins will justify sound conclusions as to the cause of changes in venous caliber. An exception to this exists in some of the better controlled microscopic studies in which attention is directed toward unique vessels in the microscopic field. In this case the observer has the advantage of being able to assess directly the rate of capillary flow as well as the caliber and flow of vessels in parallel and series with the vessel under study. The contributions of such studies of the "microcirculation" are reviewed in Chapter 27. At this point we would only stress the principle that any observer of blood vessels must be thinking in rigorous hemodynamic terms if he is to make valid inferences from his observations, and refrain from any conclusions in regard to venous tone without reasonably secure evidence that other hemodynamic factors are not the significant ones.

Inferences from Venous Pressure

It has already been emphasized that inferences about venous tone based solely on venous pressure

are virtually worthless. Large portions of the venous bed are in a state of partial collapse, in which case pressures are not conditioned by vascular tone but by the interplay of extravascular pressures with intravascular dynamics. The small magnitude of venous pressure further complicates the problem, since an adequate definition of zero reference levels, appropriate to the specific conditions of the experiment, is often extremely difficult. Finally, in situations where venomotor activity exhibits any significant change, there are usually associated changes in cardiac activity and blood flow which produce passive changes in venous pressure. These further confound any valid assessment of venous tone.

Measurement of Pressure Gradients

Errors in attempting to draw inferences from isolated venous pressure might be reduced by measuring successive venous pressures along the venous gradient in conjunction with determinations of blood flow. Unfortunately, this approach is still confronted by the obstacle of collapse phenomena, aggravated in the case of intrathoracic and intra-abdominal veins by respiratory variations in extravascular pressure. The author is not alone among investigators who have spent frustrating hours attempting to interpret pressure gradients in such veins.

An older method for surmounting this obstacle in the larger veins was introduced by Donegan (19). He selected appropriate vein segments which could be isolated and perfused artificially, at sufficient rates to keep them well distended, and could yield meaningful pressure gradients. By judicious selection of the segment to be perfused, it is possible to preserve innervation to the vein and thus study the normal venomotor responses of such a vein segment *in vivo*. This technique has yielded a great deal of significant information in the hands of Fleisch (25), Gollwitzer-Meier (35, 36), and others. Unfortunately such preparations are rather difficult to prepare and maintain in good reactive condition, perhaps due to the trauma of isolation and double cannulation, possible interferences with vasa venarum circulation, temperature changes, and other artifacts introduced by the artificial perfusion. Fleisch particularly stresses the precautions which must be observed if a reactive preparation is to be obtained. This technique can therefore only be trusted when significant positive results are obtained; it is difficult to dissociate valid negative responses from deterioration of the preparation.

Another method of avoiding the collapse problem would be to proceed out far enough into the peripheral venous system to areas of steeper pressure gradients and higher absolute pressure levels, preferably in superficial areas where one can be confident that extravascular pressures will never approach the order of magnitude of intravascular pressures. A very significant advance is therefore represented by the work of Haddy (27, 41-45) who has employed fine plastic catheters and passed them in a retrograde direction into minute peripheral blood vessels, such as those of the paw. This retrograde catheterization must avoid areas with valves. By simultaneously recording pressures from minute vessels approached from both the arterial and the venous sides, and also from the corresponding large arteries and veins, he has been able to plot the pressure gradient through the total vascular bed. When combined with flow measurements, the flow resistance of each segment of the bed may be calculated. As has been previously discussed, moderate changes in the pattern of flow resistance and pressure gradient in local segments of the peripheral venous bed may not produce any alterations in the total capillary-to-heart pressure flow gradient; yet these changes will signify alterations in venous tone and the shifts in venous capacity which presumably result. With more intense venoconstrictor responses, venous resistance may become elevated to the point that capillary pressure rises, in which case this technique also becomes a very useful adjunct to the study of factors leading to tissue edema (41).

This technique has proven quite fruitful in the analysis of the effect of a variety of agents on the peripheral venous system. One example is shown in figure 9. The upper part of this figure indicates the pressures recorded from the vessels in the foreleg of a dog that was being perfused artificially at a constant rate; below are plotted the resistances calculated from the flow and pressure gradient data. On the left of the figure, the innervation was intact and vascular tone was high, as reflected in a high arterial pressure. Administration of 5-hydroxytryptamine (serotonin) produced a significant drop in pressure and resistance on the arterial side, particularly in the smaller vessels, attributed to antagonism of the adrenergic constrictor mechanism. In contrast, there was a dramatic rise in small vein pressure, interpreted as due to a direct constrictor action of this drug on the veins. Following denervation, the right of the figure indicates a low initial pressure on the arterial side because of a loss of sympathetic tone. Under these conditions, 5-hydroxytryptamine is observed to produce a significant

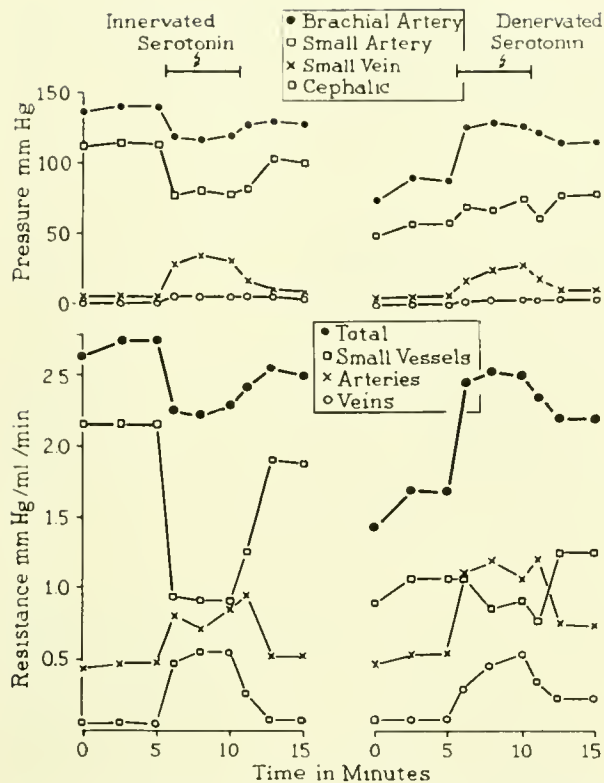


FIG. 9. Pressure gradients and resistance changes recorded from the foreleg and paw of a dog that was artificially perfused at a constant rate of flow, demonstrating the application of the Haddy technique (45).

constriction of the large arteries and veins, and only a minor change in the smaller vessel segment.

The fact that pressures in minute vessels show considerable pulsatile variation (41, 55), presumably associated with a type of venovasomotion (44), renders such measurements of greater qualitative than quantitative value, since it is difficult to have faith that the discrete vessel from which the peripheral pressure was recorded is accurately representative of the mean pressure in the peripheral venous bed as a whole. This reservation is reinforced by the possibility that the catheter might be wedged so that the recorded pressure represents that of a collateral somewhat remote from the catheter, and also the possibility that the presence of the catheter itself might alter pressure-flow dynamics. Nevertheless, if one keeps these reservations in mind, and takes precautions to be extremely critical of instrumental techniques and record analysis so as to exclude the many possible artifacts which may creep into a method of this type, this appears to be one of the most valuable techniques currently available for studying peripheral venous

function. It should be appreciated that this method also has the merits of being applicable to human studies (88).

Pressure Measurements in an Occluded Venous Segment

Doupe and associates (20) appear to have been the first to have employed the method of isolating a segment of a superficial vein between a pair of compressing wedges. If the wedges are placed so that the intervening segment is free of branches, this creates a blind cul-de-sac with an entrapped volume. If a needle is then carefully introduced into this segment, it is possible to record pressures in a system of fixed volume, hence any change in pressure must reflect a change in the muscle tone. In actual practice, it appears to be necessary to distend the vein with a considerable volume increment so as to yield basal pressures of the order of 40 to 60 cm H₂O in order to achieve significant pressure changes. This also serves the purpose of elevating the recorded pressure out of the range of confusion with extravascular pressure effects.

A recording from such a preparation is illustrated in figure 10. This illustrates one feature that is conspicuously demonstrated by this technique: the marked influence of psychic stimulation on venomotor response as the experimental subject witnesses the preparation of some experimental maneuver which he is to undergo. Since responses of the type illustrated in figure 10 disappear after sympatholytic drugs, there can be little doubt as to their venomotor origin. This technique has been exploited with considerable success (14, 68) and is the most direct qualitative method for studying the venous reactions of the human subject. Because it concerns itself with a unique venous segment, however, it does not appear feasible to standardize the quantitation of pressure responses observed in such studies.

A variation of this technique is to introduce a small cylindrical balloon into a vein segment and measure pressure changes in this balloon. This obviates the necessity of selecting a segment free of branches, and gives greater confidence that the observations are being obtained from a closed system. As with the method previously described, it also seems essential to distend the balloon to pressure of 30 cm H₂O or higher in order to observe significant changes. Salzman (81) has successfully applied this technique to the study of the venomotor response to pressoreceptor reflexes. Connolly & Wood (18), on the other hand,

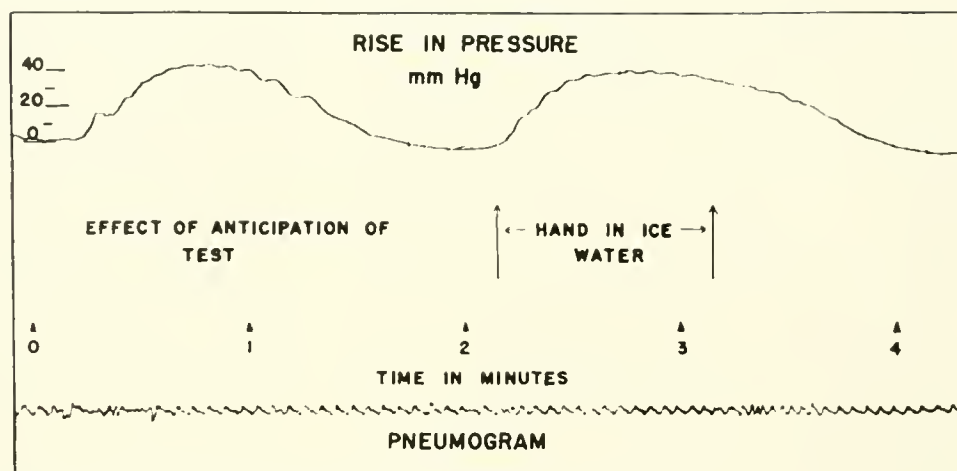


FIG. 10. Pressure changes recorded from a segment of a superficial vein of the forearm that had been isolated between wedges and kept at constant volume. [From Duggan *et al.* (21).]

were unable to record temperature reactions in superficial veins in man by this technique, even though veins adjacent to that containing the balloon exhibited obvious caliber changes. The author has similarly been unsuccessful in attempting to get sufficient response for accurate analysis in a variety of applications of this technique to various dog preparations. Further studies are in order to determine the full potentialities and limitations of this method.

Another type of method which is based on the same principle was introduced by Hooker (54) and has been adapted to human studies by Wallace (87, 88). By use of a pressure cuff on the arm, pressure is first developed to occlude venous drainage and produce venous congestion, and then further elevated to stop all blood flow to the arm. Venous pressures measured between 2 and 8 min after obstruction to blood flow show a slow decline, presumably due to capillary transudation. Venomotor stimulation produces pressure changes superimposed on this slow decline. Although this method has yielded clear qualitative evidence of venomotor reactions (64), and possibly has some merits of simplicity, it introduces a number of complicating features, such as prolonged ischemia, which would vitiate precise quantitation and therefore place it in an unfavorable position as compared with other methods that are available.

Pulse Methods

Pulsatile changes in the volume contained within a vascular segment will produce pulsatile pressure changes, the magnitude and rate of transmission of

which are determined by the elastic properties of the vessel wall. Since muscle tone is one of the factors influencing elasticity of the venous wall, this suggests another possible approach to an assessment of venomotor tone. Unfortunately, the pulsations which occur normally in the venous system are too small in magnitude and too complex in etiology to be susceptible to this type of analysis.

Peterson (72, 73) has overcome this limitation by generating pulses artificially with a high speed injection system. There results a momentary peak of pressure which increases in magnitude as venous tone increases. As yet, limited applications of this type of method have been reported. The author has had extensive experience with a related phenomenon that he has referred to as the "acceleration transient" which appears at the moment of initiating a constant speed injection into a vein. It is clear that many details at the tip of the injection cannula can influence the pressure peak produced. The exact dimensions and orientation of the injection orifice in relation to the vessel lumen are of critical importance in determining the exact pattern of pressure development, and this problem can be gravely augmented by the tendency for some veins to develop a segment of local constriction in the area of cannulation. Extending the orifice to a site somewhat remote from the point of cannulation introduces problems of proper orientation of the injection tip, and also requires pressure recording through a separate channel in order to prevent the flow resistance of an elongated injection cannula from dominating the pressure recording. Although the potentialities of such a pulse method

should not be overlooked, at present it has not been developed to the point that it can be applied to the accurate measurement of venous tone.

Venous Distensibility Patterns

As has been pointed out in reference to figure 5, constriction of a vein alters its distensibility diagram. The maximally dilated vein exhibits a smooth curve convex toward the volume axis. As progressively more constriction occurs, the distensibility curve is transformed into a sigmoid form showing initially a relatively rapid rise in pressure with initial volume increments, a very much slower pressure rise as intermediate volumes are added, and then a final steep rise in pressure as still further volume is introduced. If the rate of venous distension is carefully controlled so as to prevent stress relaxation effects from distorting the slopes of these curves, evidence of venoconstriction should be obtainable from studies of the shape of the distensibility curve.

The first application of this principle was presented by Capps (16) using a plethysmographic method on the human forearm. The use of the plethysmographic technique for venous distensibility measurements was a logical outgrowth of measurements of blood flow by the Hewlett & Van Zwaluwenburg method (50). In the latter method, while the distal portion of the arm is enclosed in a plethysmograph to record arm volume, a pressure cuff around a proximal portion is suddenly inflated to a pressure slightly less than the arterial diastolic pressure. This suddenly blocks venous outflow from the arm without any immediate interference with arterial inflow, and hence the arm will increase in volume at a rate equal to the rate of blood flow into the arm. After a short interval, this blood flow will be reduced by the progressive congestion of the distal vascular bed. The point is reached eventually where arm volume becomes relatively stable, and this must mean that venous pressure has increased to equal cuff pressure so that venous blood will be forced past the occluding cuff at a rate equal to the reduced inflow rate. As has been pointed out earlier, the most significant factor in the change in the volume of the arm under these conditions is the congestion of the venous bed (17, 39). Therefore, using stepwise increments in pressure in the occluding cuff yields a series of increments in arm volume which, as a reasonably good first approximation, represents the increase in venous volume at the corresponding occluding pressures. With this method, Capps obtained clear evidence of

a sigmoid distensibility curve in veins constricted by cold and other venoconstrictor stimuli, while dilated veins exhibited a typical convex distensibility pattern.

Many subsequent authors have reported on venomotor reactions using the plethysmographic method. A number of modifications in technique have been introduced to minimize the artifact associated with inflation of the pressure cuff, and to permit accurate pressure reference levels. Errors in the pressure-volume determinations due to unequal distribution of pressure in the transitional zone at the margin of the plethysmograph may be corrected by use of a double plethysmograph. Both compartments are exposed to equal pressures, but only the distal segment is used for volume recording (93). Burch (12) has used another method to correct for the occlusion artifact in developing the plethysmographic technique for use on the digit. By measuring the volume change produced by the venous occlusion cuff during an interval when all blood flow had been arrested by arterial compression, he obtains an uncomplicated record of the artifact alone, which can be subtracted from the blood flow curves. When these corrected curves are compared with unoccluded digital pulse curves, he feels that he can analyze arterial inflow and venous outflow dynamics with sufficient accuracy to quantitate the phasic changes that occur during each pulse wave.

Other plethysmographic devices, such as the mercury-in-rubber resistance strain gauge (89) or the impedance plethysmograph (75), may be adapted for venous studies, although the simplicity of their application should not encourage neglect of establishing their quantitative reliability.

There is one inherent difficulty in the plethysmographic method for distensibility determinations, however, which in the opinion of the author has not been adequately resolved. The sudden increment in venous outflow pressure will have its most direct effect in elevating venous pressure; to a lesser extent it will elevate capillary pressure, and to a slight extent it will elevate the distal portions of the arterial pressure gradient. This justifies the assumption that most of the immediate volume change will occur on the venous side, an assumption which has been reasonably well substantiated. On the other hand, the elevated capillary pressure promotes capillary transudation, so that the recorded volume never reaches a true plateau, but shows a slow increase persisting after the initial major increase. Owing to the time-dependent characteristics of vascular elasticity, moreover, venous distension occurs rapidly at first and

then distends more slowly toward its equilibrium condition. As a consequence, volume increase due to the delayed distension of the veins merges indistinguishably with the volume increase due to capillary leakage. One might attempt to control this problem by using rigorously standardized intervals of pressure exposure before reading the volume. Since the magnitude of the effect increases as higher pressures are reached, however (cf fig. 6), virtually all reports of the use of the plethysmographic technique have described vague and highly subjective criteria for selecting the end point at which to read the volume. There results a random scatter of the determined points which often obscures the actual form of the distensibility curve. Therefore most recent authors have abandoned any attempt to interpret the form of the curve, and base their interpretations solely on the total volume increment between two arbitrary pressure levels. We will return to consider the significance of this type of interpretation after first considering other techniques which have focused on the form of the distensibility curve.

The author has developed a method based upon the change in distensibility pattern of intestinal veins in the dog. After surgical isolation of the blood flow through an intestinal loop, the circulation is momentarily interrupted while blood is injected in a retrograde direction into the venous bed. By dividing the volume change required to raise the venous pressure from 10 to 20 cm saline into the volume change required to raise the pressure from 20 to 30 cm saline, it is possible to calculate a "venomotor index" which expresses numerically the degree of sigmoid curvature. This method has been standardized by use of a motor-driven syringe and accurate timing of the injections so that highly reproducible readings can be obtained, permitting following changes in venomotor tone in an animal over a period of several hours (5). Also, if injection rates are adjusted so as to yield equivalent rates of pressure rise in preparations of different sizes, reasonably quantitative comparisons can be made between different animals.

Unfortunately, this method is not without its limitations. There remain some unanswered questions as to the exact nature of such a retrograde injection. The method was originally designed on the assumption that there were no valves in this bed. Since India ink injections invaded the minute vessels of the viscus, and yet there was no suggestion of any rise in pressure on the arterial side of the loop, there was an empirical basis for accepting with some confidence that the distensibility measurements were representative

of the venous bed. Recognition that these veins are in fact well supplied with valves of rather poor competence (fig. 1) raises the question as to whether the valves might be making some contribution to the pattern of the distensibility curves. To admit this possibility, however, would not alter the actual interpretation of the data. The retrograde pressure required to force blood past a valve must be a function of the muscular tone in the wall of the vessel. A dilated vein should develop valvular incompetence quite readily, while a constricted vein should be able to withstand somewhat higher back pressures before developing incompetence. Such valve action might act to exaggerate the degree of sigmoid curvature in the distensibility of a constricted venous bed, but this would reinforce rather than detract from the acceptance of the degree of sigmoid pattern as an index to the degree of venoconstriction.

A more serious difficulty relates to the moderately extensive surgical preparation required in the technique for setting up the loop, which taxes the compensatory ability of the animal. Any further major manipulation, such as an open-chest procedure, often leads to deterioration of its circulatory status. This method is also restricted to the analysis of pressure-volume increments; a satisfactory quantitation of the total venous volume has not yet proved feasible. This negates some of the potential value of obtaining a quantitative index, since it cannot be related in meaningful terms to total circulatory function. Although this is a defect which this technique shares in common with most other methods for assessing the functional activity of the peripheral venous bed, it is important not to lose sight of the ultimate goal of being able to evaluate quantitatively the contribution of the peripheral venous bed to over-all circulatory dynamics.

A further extension of this general method has recently been introduced by Bartelstone (7), who has studied the pattern of pressure development behind a sudden obstruction of the vena cava. His results also afford evidence of the sigmoid distensibility pattern which develops with venous constriction, although in this method the quantitative interpretation is complicated by simultaneous changes in flow.

Distensibility by Volume Increment

As implied above, the plethysmographically recorded distensibility of the venous bed has been subjected to two types of interpretation. Capps stressed the pattern of the data, with the constricted veins showing relatively less distensibility at low pressures

and greater distensibility at intermediate pressures. A majority of authors, however, have stressed the increment in volume between two arbitrary pressures, and interpreted a decrease in the volume change between these two pressures as an indication of venous constriction.

To argue that a decreased volume increment is an indication of venoconstriction might appear to represent a conflict with our previous discussion of distensibility patterns. The great distensibility of the constricted vein over the intermediate range of the sigmoid curve would seem to demand a great total distensibility in the constricted vein. As can be appreciated by reference back to figure 5, however, a comparison of the volume increments in constricted and dilated veins between any two arbitrary pressures will yield different relationships at different pressure levels. In the experiment shown in figure 7, for example, the injection happens to have been stopped at the point that the pressure-volume relationships in the constricted and dilated veins were virtually identical; a comparison of the total pressure-volume increment would offer no suggestion of the significant differences in distensibility above and below this particular point.

The author is not aware of any data, obtained with sufficient precision to identify the pattern of the distensibility curve, in which apparent discrepancies in the interpretation of decreased venous distensibilities cannot be resolved by reference to the pressure level. To illustrate this point, the data in figure 11 were taken from a report of a reasonably well-standardized application of the plethysmographic method and described by the authors as a "typical" response.

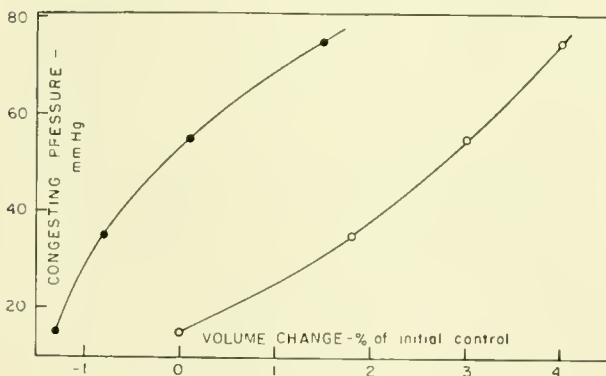


FIG. 11. Volume increments in the human forearm recorded by congesting the veins to successively higher pressure. Open circles indicate control values; solid circles are the volumes determined while infusing noradrenaline at the rate of 0.4 $\mu\text{g}/\text{min}$. [Redrawn from Glover *et al.* (34).]

The authors interpreted these data as demonstrating that noradrenaline acts to decrease venous distensibility. One cannot argue with such an interpretation as a correct description of the data as far as they go. Nonetheless, this interpretation ignores the different form of the curves. Although the control data exhibit a relationship convex to the volume axis, the data recorded during noradrenaline infusion are clearly concave to the volume axis. These data are therefore completely compatible with the pattern interpretation used by Capps and generalized in figure 5. An extrapolation of the curves in figure 11 to higher pressures would clearly lead to a relative increase in the total distensibility of the constricted vessels and a relative decrease in the total distensibility of the dilated vessels. Unfortunately, since the plethysmographic method cannot be used effectively when venous congesting pressures approach arterial pressures, this technique does not appear suitable for bringing out the full sigmoid distensibility pattern in these veins. It should be recognized that veins in the extremities are subjected to much greater hydrostatic loads than are visceral veins, and therefore it would not be at all surprising to discover that much higher pressures were required to achieve the full sigmoid pattern in arm veins.

It is of interest to note that a similar argument has arisen in reference to isolated vein preparations. Leonard & Sarnoff (59) state unequivocally that a constrictor drug always reduces venous distensibility. Inspection of the Leonard and Sarnoff report, however, reveals a definite alteration of the pattern of their distensibility data which is quite compatible with the suggestion that sufficient stretch will eventually reveal a very significant distensibility of the constricted vein.

Nevertheless, there is another factor in these distensibility characteristics which must be considered. The original interpretation of the sigmoid curve visualized that at high pressures the constricted vessel was pulled out to the same dimension as the dilated vessel, and thus demands that the total distensibility must be greater in the constricted vessel. As has been discussed earlier, the validity of this interpretation is open to some question. It is conceivable that a sigmoid distensibility pattern may be compatible with some reduction in total distensibility. If, in addition, dilated veins were in a state of partial collapse at the point that the initial volume was measured, this would augment the possibility of observing a greater total distensibility in the dilated vein.

One is therefore justified to interpret distensibility data in whatever fashion appears compatible with the responses observed with his particular method. Since there is overwhelming evidence that adrenergic drugs are potent venoconstrictors, a reproducible response to such drugs may be used as a reference standard to which responses evoked by other stimuli may be related. It would nonetheless be desirable to adopt accurately standardized methods for distending veins so that data will have greater validity. In view of the significant stress relaxation and creep phenomena demonstrated by veins, one can scarcely hope to obtain any precise information by making measurements "as soon as the volume seems reasonably stable."

SUMMARY OF VENOMOTOR RESPONSES

From the great variety of techniques that have been employed for the assessment of venomotor activity, a wealth of information has been obtained which demonstrates at least qualitatively the types of stimuli which evoke venomotor responses. In table 1 are listed responses which stand without controversy as representative of the active responses of the venous system. It should be understood that this listing does not pretend to be comprehensive or cover any significant fraction of the full literature on the subject; in general it has proven convenient to confine the citations in this table to reports which have been referred to for other purposes in our previous discussion. This evidence of a broad spectrum of reactivity suggests that the venous system must play an important function in active regulation of the circulation as a whole. For a discussion of this important aspect of venomotor action, the reader is referred to Chapter 32. The remainder of our comments will be confined to response characteristics which appear to be of some unique importance to the venous system.

Most investigators of the venous system have been impressed with the fact, first emphasized by Gollwitzer-Meier (36), that the venous system appears to act synergistically with the arterial system. This is emphasized in the evidence presented in table 1; with the exception of histamine, all responses listed are direct counterparts of similar reactions known to occur on the arterial side of the circulation. Beyond this qualitative similarity, the interesting question arises as to the relative sensitivity of arteriomotor

TABLE 1

| <i>Venoconstrictor Responses</i> | <i>References</i> |
|----------------------------------|----------------------------------------------------------|
| Adrenergic drugs | 2, 4, 14, 19, 25, 34, 40, 43, 59, 61, 63, 82, 88, 91, 93 |
| 5-Hydroxytryptamine | 34, 43, 45 |
| Histamine | 25, 61 |
| Carotid sinus hypotension | 4, 5, 68, 81 |
| Hypercapnia (central) | 4, 21, 35, 54 |
| Hypoxia | 4 |
| Cold | 16, 20, 39, 42, 56, 68, 88, 93 |
| Deep inspiration | 14, 21, 64 |
| Intense sensory stimulation | 4, 8, 54 |
| Psychic stimulation | 14, 21, 68 |
| Exercise | 41, 64, 68 |
| <i>Venodilator Responses</i> | |
| Nitrites | 61, 91, 92 |
| Acetyl choline | 25 |
| Adenylic acid | 3 |
| Carotid sinus hypertension | 4, 68, 81 |
| Neurogenic syncope | 14 |
| Sleep | 14 |

and venomotor systems. The literature contains definite suggestions that the venous system may have a greater sensitivity (55, 92) and also make a greater contribution to the total circulatory response (53), although more information is needed to permit sound generalizations.

There are a few instances, however, in which the responses of the venous system appear to be unique. One is the influence of 5-hydroxytryptamine previously discussed in reference to figure 9. Haddy's data would indicate that this compound is more effective in producing venoconstriction than it is in blocking pre-existing venous constriction resulting from high sympathetic tone, while for the small vessels on the arterial side of the circulation, the sympathetic blockade can dominate the direct constrictor action of the compound. Therefore, 5-hydroxytryptamine shares with histamine the capacity to produce both venoconstriction and arteriolar dilation; as a consequence both of these compounds have the capacity to induce edema formation. There is an indication that local tissue acidity may also have such an action (27, 32). An inverse type of dissociation between arterial and venous effects has been reported to occur in circulatory shock, where venoconstrictor mechanisms fail at a point at which arterial constrictor tone is still well maintained (5).

A particularly interesting dissociation also appears to exist in reference to temperature effects. While cold produces significant constriction of cutaneous arterioles, it is even more effective as a venoconstrictor

tor. This cold venoconstriction has a significant reflex basis as well as a local component (18). As a consequence, capillary pressure should rise, accounting for the increased transudation of fluid and the tendency for the hematocrit to rise in cold. Secondly, the fall in temperature so interferes with dissociation of oxyhemoglobin as to produce some tissue anoxia. The anoxic metabolites tend to act as vasodilators competing with the cold constriction of the arterioles, but seem to have no capacity to cause venodilation. As a consequence, the skin becomes plethoric because of some arterial inflow in the face of a continued resistance to venous outflow. Rewarming of the tissue will now cause arteriolar dilation. There is considerable evidence, however, that the veins do not dilate in response to heat (39, 42, 56, 93). Indeed, the extreme venoconstriction produced by the previous cold stimulus seems to dissipate slowly after the tissue is rewarmed, so that during the initial phase there is significant arteriolar dilation in spite of persisting venous constriction (42). This accounts for the extreme degree of plethora and tendency toward edema formation which is observed in the rewarming phase.

Finally, attention should be called to fragmentary information relating to the possibility of venovenous reflexes. Apart from the general homeostatic regulators of the circulation, such as the arterial pressoreceptor mechanism and the chemoreceptor responses, are there mechanisms for adjusting venous capacity as a function of the venous pressure? In view of the importance of the central venous pressure in determining cardiac output, circulatory homeostasis would be enhanced if there were such a mechanism for adjusting venous capacity to central venous pressure, so that the venous reservoir tended to expand in response to an increase in venous pressure and contract in response to a decrease in venous pressure.

There are several suggestions that such a mechanism exists. With acute hypotension produced by vagal bradycardia, Fleisch (26) observed an initial venous constriction, attributable to the carotid sinus reflex, followed by a secondary venous dilation which he felt was associated with the venous congestion produced by the bradycardia. A very similar observation was reported by Schretzenmayr (82) in the response to adrenergic drugs. Although these drugs usually produced a conspicuous venoconstriction, in instances where the circulatory load became so great as to momentarily embarrass the heart and produce cardiac distension, there appeared

to be some mechanism that was counteracting the venous constriction. More direct evidence of this mechanism has been provided by the author (6), who demonstrated venodilation to be produced reflexly when venous congestion was produced by inflating a balloon in the thoracic vena cava. It is important to note, however, that to demonstrate this effect it proved quite essential to prevent changes in pressure on the arterial side of the circulation. Unless such precautions are taken, the arterial pressoreceptor system dominates the circulatory responses, and the venovenous reflex mechanism described above is completely overwhelmed.

This dominance of the arterial pressoreceptor reflexes accounts for a number of observations which otherwise would argue against the venovenous reflex. Wood (93) has demonstrated reflex venous constriction in man associated with venous congestion produced by occluding cuffs on the extremities. Inasmuch as they observed a reflex tachycardia as well as arterial constriction associated with what was estimated to be a 15 per cent reduction in circulating blood volume, this response would relate primarily to arterial pressoreceptor mechanisms. In confirmation of this, when the subjects were in a supine position so as to minimize pooling of blood with venous tourniquets, neither the venous reflex nor other signs of compensation to arterial hypotension were observed. Similarly, Page and co-workers (68) found venoconstriction to be produced by the Valsalva maneuver, which would also be explainable in terms of baroreceptors on the arterial side dominating the simultaneous effects of congestion on the venous side.

There remains the problem of interpreting the evidence presented by Burch (13) that patients in congestive heart failure are characterized by an augmented venomotor tone. If one assumes that the only significant feature in this condition is venous distention, this finding would not be compatible with the postulation of a reflex venodilation in response to venous distension. It may be of significance that Burch found definite evidence of venoconstriction only in those patients who were rather severely decompensated and in whom numerous other sources of reflex stimulation might therefore have been operable. Our inability to define more clearly the exact nature of the venomotor reactions occurring in such an important clinical problem should afford adequate stimulus to seek still further clarification of the nature of venomotor control.

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Venous return

ARTHUR C. GUYTON

*Department of Physiology and Biophysics, University of Mississippi
School of Medicine, Jackson, Mississippi*

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Summary

INTRODUCTION

THE TERM "VENOUS RETURN" means very simply the flow of blood from the veins into the heart, and this, obviously, can be divided into "systemic venous return" and "pulmonary venous return." The function of the veins and the importance of venous return have been covered from different points of view in several important monographs (31, 70) and reviews (72, 82–85, 133, 137). Also, the basic characteristics of the veins as blood vessels are reviewed by Alexander in Chapter 31. Therefore, the purpose of this chapter will be to discuss especially the regulation of venous return and secondarily the associated factor venous pressure.

Though the venous return is normally exactly equal to ventricular output, this may not be true for short periods of time. However, when the venous return is greater than the ventricular output, blood will accumulate in the heart. During the ensuing few heartbeats a new state of equilibrium will develop, and venous return will again become equal to the output. Yet, since there are times when venous return and cardiac output are not equal, it is justified to use the term "venous return" separately from the term "cardiac output."

Normally, in speaking of cardiac output, one thinks principally of cardiac activity, whereas in speaking of venous return, he thinks of all the functions of the peripheral circulation that have to do with blood flow into the heart. For this reason many circulatory physiologists consider cardiac output to be regulated principally by the heart and venous return to be regulated principally by peripheral factors. By all means, the reader must be cautioned at the outset against this viewpoint, because except for instantaneous periods of time, any factor that affects cardiac output also affects venous return, and any factor that affects venous return also affects cardiac output. This principle can be expressed in another way: The circulatory system is a circuit, and the total flow of blood through any one cross section of the circuit is exactly the same as the total flow through any other cross section.

Principles of Circuit Analysis as They Apply To Venous Return

Often, physiologists have attempted to analyze the regulation of venous return entirely on the basis of local factors in the veins and right heart. However, this is a completely fallacious approach, for any factor that affects blood flow in any single unit of the entire circulation will likely at the same time affect venous return. For this reason, a complete circuit analysis of the entire circulation is required for any degree of accuracy in determining the factors that regulate venous return (46, 47, 78, 81, 126-128, 192). This means that the same factors that regulate cardiac output are those which also regulate venous return. In general, these can be divided into two major groups: those concerned with the ability of each side of the heart to pump blood, and, second, those concerned with the ability of blood to flow through the two divisions of the peripheral circulation, the systemic circulation, and the pulmonary circulation. In this chapter we will be concerned with both of these groups of factors and with the manner in which they

operate together to regulate blood flow in the circulation. However, the contribution of the heart to the regulation of blood flow in the circulation is discussed in great detail in several other chapters, including especially those by Hamilton, Sarnoff & Mitchell, Brecher, and Rushmer (Chapters 17, 15, 23, and 16, respectively). Therefore, in this chapter we will discuss the cardiac factors only briefly while discussing the peripheral factors in far greater detail.

THE PROBLEM. Figure 1 depicts a highly simplified diagram of many of the important factors that must be considered in analyzing blood flow around the circulatory circuit. First of all, we note in the diagram the term blood flow (F) appearing at four different points: 1) at the output of the right heart, 2) at the output of the pulmonary circulation, 3) at the output of the left heart, and 4) at the output of the systemic circulation. Under steady-state conditions, the blood flow at all of these four points will be exactly equal. Yet, in a circulatory analysis we must consider them separately, because they are not always equal, and during the periods of time when they are unequal, blood will be actively translocated from one part of the circulation to another, thus causing new equilibrium conditions to develop. Now to describe the

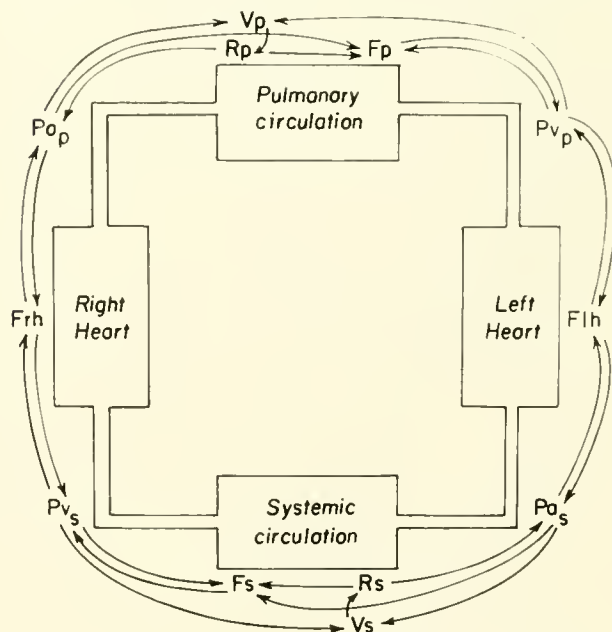


FIG. 1. Circulatory schema, showing the effects of individual factors in different parts of the circulation on other functions of the circulation. Each arrow represents a separate effect, and a composite analysis of the circulation requires that all these effects be considered simultaneously as explained in the text.

events depicted in figure 1, we can start by pointing out that each arrow represents an effect of one factor on another factor. The different effects denoted in this figure can be listed as follows:

- (1) Right heart blood flow (F_{rh}) directly affects pulmonary arterial pressure (P_{ap}).
- (2) Right heart blood flow (F_{rh}) inversely affects systemic venous pressure (P_{vs}).
- (3) Pulmonary arterial pressure (P_{ap}) inversely affects right heart blood flow (F_{rh}).
- (4) Pulmonary arterial pressure (P_{ap}) directly affects pulmonary blood volume (V_p).
- (5) Pulmonary arterial pressure (P_{ap}) directly affects pulmonary blood flow (F_p).
- (6) Pulmonary blood volume (V_p) inversely affects pulmonary resistance (R_p).
- (7) Pulmonary resistance (R_p) directly affects pulmonary arterial pressure (P_{ap}).
- (8) Pulmonary resistance (R_p) inversely affects pulmonary blood flow (F_p).
- (9) Pulmonary blood flow (F_p) directly affects pulmonary venous pressure (P_{vp}).
- (10) Pulmonary venous pressure (P_{vp}) directly affects pulmonary blood volume (V_p).
- (11) Pulmonary venous pressure (P_{vp}) inversely affects pulmonary blood flow (F_p).
- (12) Pulmonary venous pressure (P_{vp}) directly affects left heart flow (F_{lh}).
- (13) Left heart blood flow (F_{lh}) inversely affects pulmonary venous pressure (P_{vp}).
- (14) Left heart blood flow (F_{lh}) directly affects systemic arterial pressure (P_{as}).
- (15) Systemic arterial pressure (P_{as}) inversely affects left heart blood flow (F_{lh}).
- (16) Systemic arterial pressure (P_{as}) directly affects systemic blood volume (V_s).
- (17) Systemic arterial pressure (P_{as}) directly affects systemic blood flow (F_s).
- (18) Systemic blood volume (V_s) inversely affects systemic resistance (R_s).
- (19) Systemic resistance (R_s) directly affects systemic arterial pressure (P_{as}).
- (20) Systemic resistance (R_s) inversely affects systemic blood flow (F_s).
- (21) Systemic blood flow (F_s) directly affects systemic venous pressure (P_{vs}).
- (22) Systemic venous pressure (P_{vs}) inversely affects systemic blood flow (F_s).
- (23) Systemic venous pressure (P_{vs}) directly affects systemic blood volume (V_s).
- (24) Systemic venous pressure (P_{vs}) directly affects right heart flow (F_{rh}).

Now we have completed the circuit, giving most of the major factors within the circulation that affect each other; obviously, a change in any one of these will change all the others. However, this has been a highly simplified schema, for, onto these basic mechanical factors, we must superimpose the effects of

circulatory reflexes, hormones, special conditions such as exercise, hemorrhage, myocardial infarction, or any other condition that can affect the function of any single segment of the circulation.

To complicate the picture further, we must also note how greatly simplified some of the individual effects illustrated in figure 1 have been made. For instance, one of the effects noted in this figure is the direct effect of systemic venous pressure on right heart blood flow. Actually, the systemic venous pressure does not directly affect the right heart blood flow but instead affects the filling of the right heart. This in turn affects the degree of stretch of the cardiac musculature, which then affects the force of contraction. Finally, it is this force of contraction that directly affects the right heart blood flow. Thus, it can be seen that four steps have actually been compressed into one in the simplified diagram of figure 1.

We can summarize the problem, therefore, by pointing out that the regulatory factors of the circulatory system can be divided into literally hundreds or even thousands of individual factors distributed throughout the circulation. Indeed, even closure of a single capillary exerts its infinitesimal effect on the functions of all other parts of the circulation. This, then, is the problem with which we are faced in this chapter, to unravel the myriad of different factors that affect blood flow in the circulation and to determine those that are especially important in relation to venous return.

SOLUTION TO THE PROBLEM. Several reasonably satisfactory solutions to the above problem have now been offered, and all of them have taken the same general form [Guyton (81), Grodins (78), Warner (192)]. First, in each of the solutions, many or most of the parallel segments of the circulation are grouped together. For instance, in a general solution of the problem one would not attempt to analyze the effect of occluding each single arteriole on the circulatory dynamics, but, instead, all of the arterioles are grouped together. Similarly, the capillaries are grouped together, the venules, the large arteries, the large veins, and so forth. This is done separately for the systemic circulation and pulmonary circulation. The next step in the solution is to group the individual segments of the circulation into several convenient larger segments and then to analyze the function of each of these larger segments separately, this followed by a synthesis of the separate analyses into a composite analysis. Thus, as we shall show later in the chapter, the function of the right heart can be analyzed sepa-

rately; then the function of the pulmonary circulation can be analyzed; then that of the left heart, and that of the systemic circulation. Once these four analyses have been made they can be put together either algebraically or graphically to derive a composite analysis of the entire circulation. In a still further simplified analysis one can even analyze the function of the entire heart and pulmonary circulation as a single segment of the circulation, such as is usually done in studying the heart-lung preparation. Then the systemic circulation can be analyzed as a separate segment and the two analyses put together to provide a composite analysis for the entire circulation.

Obviously, the more extensively the different parts of the circulation are grouped into large circulatory segments the less accurate becomes the over-all analysis. Furthermore, the type of analysis and the type of grouping of circulatory segments that will be used will depend to some extent on the factors of the circulation and the type of circulatory stress one wishes to study. Fortunately, it is usually possible to find some specific grouping of circulatory segments that is both simple and yet accurate enough for the desired purpose.

The Classical Analysis of Venous Return— Vis a Tergo and Vis a Fronte

The classical method for analyzing the factors that affect venous return has been to consider that two forces affect blood flow from the systemic veins into the right atrium (31, 70, 132, 133): 1) the force from behind, called "vis a tergo," which pushes blood along the veins toward the right atrium, and 2) the force from in front, that is, from the right heart itself, called "vis a fronte," which either impedes blood flow into the heart or perhaps at times aids the flow. Actually, the vis a tergo is the force that remains after dissipation of the arterial pressure during the course of blood flow through the systemic vessels. Conversely, the vis a fronte is a back pressure from the heart that depends principally on the over-all pumping activity of the heart. If the heart is very active as a pump, the back pressure will be low and consequently the vis a tergo can force blood into the heart with ease. Conversely, if the pumping activity of the heart is weakened, then the back pressure from the heart will be greatly enhanced, this in turn impeding the flow of blood into the heart.

A specific factor that must be considered in relation to the vis a fronte is the possibility of suction of blood into the heart caused by relaxation of the cardiac

chambers or caused by respiratory movements, and a vast segment of the literature on venous return has concerned itself with these considerations. They will be discussed in detail in the latter part of the chapter.

History of More Complete Circulatory Analyses

Unfortunately, the classical analysis of venous return has never been quantitative because such a simple presentation does not provide an adequate basis for delineating either the many different peripheral or cardiac factors that affect vis a tergo or those that affect vis a fronte. For this reason, progressive attempts have been made—very slowly, to be sure, but beginning about one hundred years ago—to provide more complete analyses of the circulation, with consequently higher degrees of quantitation of the interrelationships between the individual circulatory factors. The first real attempt in this direction seems to have been made by Weber (194) in 1850, at which time he expressed in general the complexity of the relationships illustrated in figure 1, though not expressing these in precisely the same manner as shown here. From the literature it is equally as evident that these general principles have been well understood by Starling (179), Bolton (23), Starr (180, 182), Katz *et al.* (126–128), Daly *et al.* (46, 47), Rose *et al.* (168), and Rashkind *et al.* (158). Yet, it has been only in the last half decade that serious attempts have been made to provide composite analyses of the circulation. From our laboratory has come a graphical approach to this problem (81), both in a simplified version and in a more complex version, portions of each of which will be presented in this chapter. In addition to this, two different and closely similar algebraic analyses have been presented by Grodins (78) and by Warner (192). All these analyses are based on the general principles illustrated in figure 1. However, each of the analyses groups the components of the circulation somewhat differently, they go to greater or lesser degree into the details of either cardiac or peripheral circulatory factors, and they make slightly different basic assumptions. Yet, the results of these three entirely independent and different analyses are almost exactly identical. For this reason they all deserve the highest degree of consideration. Since each of these analyses is relatively complex and long, it would be impossible to present them all in this chapter. Therefore, this chapter will be limited to a presentation of the graphical analysis, and the serious student of this subject will be referred to the very complete and interesting algebraic analysis by

Grodins (78) and also to Chapter 50 by Warner in this *Handbook*, as well as to the paper presenting his algebraic analysis (192). The algebraic method of circuit analysis depends upon expressing the functions of the individual segments of the circulation in terms of mathematical equations. Then, for a composite analysis of the entire circulation, the equations are solved by standard methods for simultaneous equations.

SIMPLIFIED GRAPHICAL ANALYSIS OF VENOUS RETURN, CARDIAC OUTPUT, AND RIGHT ATRIAL PRESSURE

A simplified method for graphical analysis of venous return, cardiac output, and right atrial pressure depends upon dividing the circulatory system into two major segments. The first segment is a composite of the right heart, the lungs, and the left heart. The second segment is the systemic circulation. By studying flows and pressures at different points while stressing the circulation in any one of many different ways, one can analyze the circulatory functions of the heart-lung segment in *a*) the heart-lung preparation, or *b*) the intact animal. On the other hand, the functional characteristics of the systemic circulation can be studied *a*) in an isolated systemic system in which the entire heart or part of the heart is replaced by a pump (98), or *b*) in the intact circulation by measuring pressures and flows at different points while stressing the circulation. These studies yield graphical function curves that are complements to each other. These complementary curves can then be plotted on the same coordinates and thus solved by their points of intersection. The function curves depicting function of the heart-lung segment are called "cardiac output curves," and they are one form of Starling's curves of the heart. The curves depicting function in the systemic circulation are called "venous return curves." Before we can proceed further with this analysis we must now characterize the various types of cardiac output and venous return curves that occur in different circulatory conditions.

Cardiac Output Curves

In figure 2, the middle curve represents the normal cardiac output curve of the heart of a 10-kg dog. The shape of this curve has been confirmed by numerous investigators, beginning with Patterson & Starling (154) in 1914 and extending through studies by Katz (123), Krayer (131), and especially Sarnoff and his

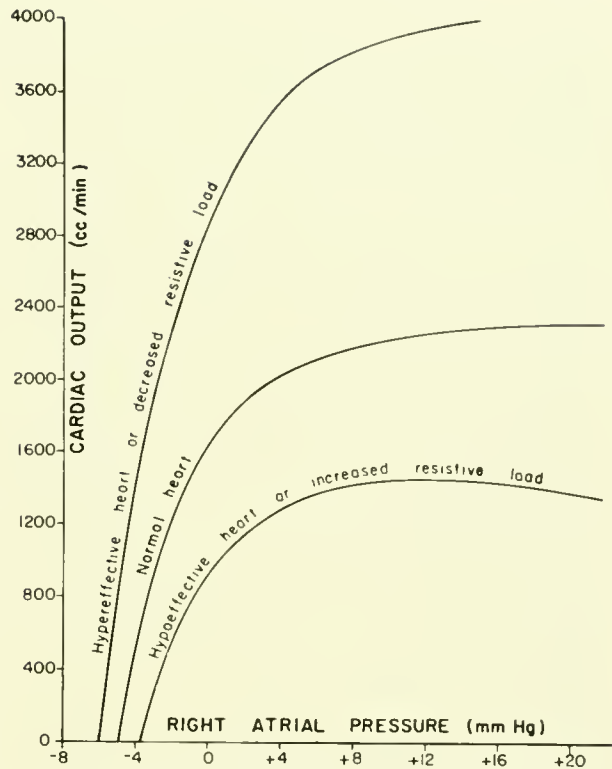


FIG. 2. Cardiac output curves for the normal heart, for hyper- and hypoeffective hearts, and for hearts subjected to increased or decreased resistive loads.

colleagues (18-20, 38, 120, 171, 172). The quantitative values used in this graph were derived principally from the original quantitation made by Patterson and Starling, data presented by Sarnoff and his colleagues, and many measurements made in our own laboratories.

A particular problem in determining the quantitative values for the cardiac output curves has been the fact that almost all such curves have been recorded in open-chest animals. Yet, in circuit analysis we need to know the quantitative values for the cardiac output curves in the normal closed-chest animal rather than in the open-chest animal. We shall see below that the quantitative values for the curves change markedly upon opening the chest. The figures expressed in this chapter will be for the closed-chest animal unless otherwise specified, and the quantitative values that are presented are based upon curves obtained in open-chest animals but extrapolated to the closed-chest animal on the basis of unpublished determinations that we have made in this laboratory while stressing the circulation with rapidly increasing or decreasing blood volume.

Basically, three different groups of factors determine

the shape and quantitative values of the cardiac output curve. These are 1) the effectiveness of the heart as a pump, 2) the pressure against which the heart must pump, and 3) factors that affect the pressure on the outside of the heart.

EFFECTIVENESS OF THE HEART AS A PUMP. When the effectiveness of the heart as a pump increases, the cardiac output curve correspondingly increases, as illustrated by the upper curve of figure 2. That is, for any given right atrial pressure the cardiac output is considerably greater from the "hypereffective" heart than from the normal heart. There are only three major causes of a hypereffective heart; these are: 1) stimulation of the heart by the sympathetic nervous system, 2) inhibition of the parasympathetic nerves to the heart, and 3) hypertrophy of the heart. In each one of these instances the heart contracts with increased force or increased rate and consequently pumps more blood for any given input pressure than does the normal heart.

Figure 2 also illustrates the effect of a hypoeffective heart on the cardiac output curve. That is, for any given input right atrial pressure, the hypoeffective heart pumps far less blood than does the normal heart. Among the different factors that can cause a hypoeffective heart are *a)* myocardial infarction, *b)* coronary sclerosis, *c)* myocarditis, *d)* valvular heart disease, *e)* congenital heart disease, *f)* cardiac arrhythmias, *g)* hypothermia, *h)* abnormal electrolytes in the extracellular fluids, *i)* parasympathetic stimulation, *j)* sympathetic inhibition, or any other factor that reduces the ability of the heart to pump blood.

Obviously, there can be all degrees of hypereffectiveness or hypoeffectiveness of the heart. Therefore, an infinite number of curves would be required to depict the various degrees of pumping effectiveness of the heart under all different conditions. Yet, at any given instant in the life of the heart, there is only one of these curves which depicts its instantaneous pumping effectiveness.

ALTERATION OF THE LOAD AGAINST WHICH THE HEART MUST PUMP. It is quite obvious that the greater the resistance against which the heart must pump blood, the less effectively can it pump (171). Consequently, increased resistive load in either the pulmonary or systemic circulation decreases the cardiac output curve, while decreased resistive load increases the cardiac output curve. These effects are also illustrated in figure 2.

Obviously, cardiac load can vary through all differ-

ent degrees at different times. Therefore, once again a vast "family" of cardiac output curves is required to depict the effects of varying loads on the function of the heart-lung segment. This family of curves is almost identical with that which depicts the functional characteristics of the hypereffective versus the hypoeffective heart.

ALTERATIONS IN PRESSURE ON THE OUTSIDE OF THE HEART. The degree of filling of the heart is determined by the effective filling pressures of the cardiac chambers, that is, by the differences between the pressures inside the cardiac chambers and the pressure on the outside of the heart. Ordinarily, the heart is surrounded by the negative pressure of the intrathoracic cavity and this negativity contributes greatly to the effective filling pressure. However, at times the negative pressure becomes altered or completely lost. For instance, opening the chest immediately shifts the heart from negative pressure surroundings to zero pressure surroundings (atmospheric pressure). And, even more important, pericardial fluid (145, 157), pericardial constriction (25), intrapleural fluid, pneumothorax (186), or mediastinal compression can all cause intensive positive pressure on the outside of the heart, thereby markedly reducing the effective filling pressures of the cardiac chambers.

In circuit analysis, an increase in the external pressure on the heart is an extremely important consideration for the following very simple reason: The resultant changes in filling pressures are not compensated by simultaneous changes in pressure in the systemic circulation. As a consequence, venous return ordinarily becomes greatly reduced.

Figure 3 illustrates the effects of opening the chest and of cardiac tamponade on the cardiac output curves. Simply opening the chest shifts the entire curve approximately 5 mm Hg to the right because of loss of the normal 5 mm Hg negative pressure in the intrathoracic cavity. This means that for the heart to pump an equivalent amount of blood after opening the chest as before, the right atrial pressure must be increased 5 mm Hg, thus explaining the detrimental effect of opening the chest on blood flow in the circulation.

The lowest curve of figure 3 illustrates even more drastic depression of the cardiac output curve, this time caused by severe cardiac tamponade. Because in this condition the intrapericardial pressure rises as the heart fills to greater volumes, the curve is not simply shifted to the right as one might have expected, but its slope and its maximum value are also reduced,

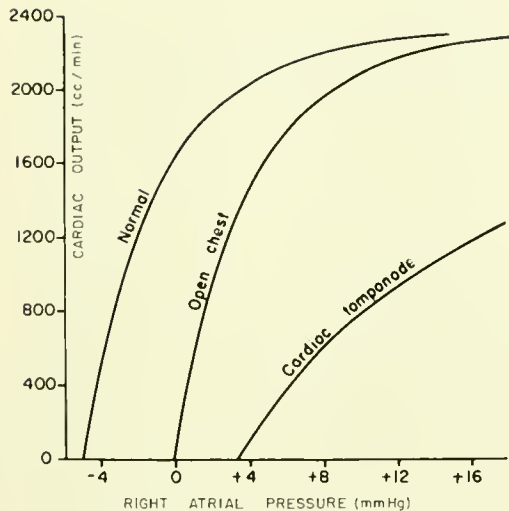


FIG. 3. Cardiac output curves, showing the effect of opening the chest and of cardiac tamponade.

the degree, of course, depending upon the degree of cardiac tamponade.

SUMMARY OF FACTORS THAT AFFECT THE CARDIAC OUTPUT CURVES. From the above discussion of the different factors that affect cardiac output curves, we see that the curves fall into two simple patterns. First, any factor that increases the effectiveness of the heart as a pump or decreases the load against which it must pump will elevate the curves. Conversely, any factor that decreases the effectiveness of the heart as a pump or increases its load will depress the curves. The second pattern of cardiac output curves occurs when pressure on the outside of the heart alters the effective cardiac filling pressures. The greater the pressure outside the heart, the further to the right is the cardiac output curve shifted.

By keeping these basic principles in mind one can determine with relative accuracy what the cardiac output curve of any given heart under any given condition will be, but it must always be remembered that at any instant the pumping effectiveness of the heart is depicted by only a single cardiac output curve, not by a family of curves. With this discussion of cardiac output curves as a background, we can now proceed to the somewhat more complicated venous return curves which are the "complements" to the cardiac output curves.

Venous Return Curves

VENOUS RETURN CURVES AS COMPLEMENTS TO CARDIAC OUTPUT CURVES. Referring back to figures 2 and 3, one

sees that each cardiac output curve represents an infinite series of cardiac outputs over a range of right atrial pressures. However, it is obvious that the cardiac output at any given time can be only one value, not an infinite number of values. The next question that arises is, how does one determine where on the cardiac output curve the circulatory system will be operating at a given time? Obviously, if one can determine the right atrial pressure, he can then determine the cardiac output. However, the right atrial pressure, like the cardiac output, is a variable. For this reason, we must find some method to determine the right atrial pressure at the same time that we determine the cardiac output. A method for doing this is to analyze the systemic circulation in terms of right atrial pressure and flow, just as the heart-lung segment has been analyzed for right atrial pressure and flow. This time we use the term "venous return" for the flow, but we still use right atrial pressure as the opposite coordinate. If we remember that venous return equals cardiac output except for transient instantaneous differences, we see that we are using exactly the same coordinates for analyzing the characteristics of the systemic circulation as we have used for the heart-lung segment of the circulation. Once this is done, the curves depicting the respective functions of the two segments of the circulation can be plotted on the same coordinates, and the point at which the two curves cross provides a solution that gives the venous return, the cardiac output, and the right atrial pressure, all simultaneously (81).

METHOD FOR RECORDING VENOUS RETURN CURVES. To determine the effect of right atrial pressure on the return of blood from the systemic circulation to the heart, we must use one of three different procedures: 1) isolate the systemic circulation and use a controlled pump in place of the heart, 2) control the action of the heart itself by placing a controlled pump in place of one portion of the heart, or 3) make measurements of flows and pressures in different parts of the systemic circulation while artificially altering the pumping ability of the heart. In our laboratory, we have studied the effect of right atrial pressure on venous return using all these three different methods, in open-chest animals when using the first two methods (87, 96, 98, 99, 102, 103, 105) and in closed-chest animals when utilizing the third method (97). The results have been identical within the limits of experimental error. Furthermore, contrary to the effects on the cardiac output curve, opening the chest

does not significantly alter the effect of right atrial pressure on venous return.

Figure 4 illustrates one of the typical methods used to study venous return. This procedure substitutes an external perfusion circuit for the right heart. The right atrium is cannulated, and blood is pumped from this cannula through a system that includes *a*) a collapsible tube that can be raised or lowered to adjust the right atrial pressure, *b*) a heater used to maintain a normal blood temperature, *c*) a pump that always provides sufficient propulsive force to keep flowing through the circuit all the blood that is allowed to pass the collapsible tube, and *d*) a recording flowmeter, usually of the rotameter type. After passing through this external circuit, the blood is reinfused into the distal stump of the pulmonary artery. Thus, all the blood entering the right atrium must pass through this external circuit. This system allows continuous recording of the blood flow through the heart, which can be termed either "venous return" or "cardiac output." Indeed, even all the coronary blood flow, which empties into the right atrium, courses through this circuit. Furthermore, the pressure inside the collapsible tube automatically adjusts exactly to the atmospheric pressure; therefore, the right atrial pressure can be elevated or lowered and maintained at a very exact value, regardless of how much blood flows into the right atrium, by simply raising or lowering the collapsible segment.

Still another important feature of this system is that the right atrial pressure, except during periods of measurements, can be maintained at a negative value, thus allowing blood to flow from the extrathoracic veins into the right atrium with equally as much ease

as in the closed-chest animal. Therefore, in using this preparation, the circulatory system does not deteriorate, as is usually the case when the veins are cannulated (178), but, instead, will continue in an active state for many hours.

EFFECT OF RIGHT ATRIAL PRESSURE ON VENOUS RETURN—THE NORMAL VENOUS RETURN CURVE. Figure 5 illustrates the normal effect on venous return of increasing the right atrial pressure (96). Note that this curve, like the cardiac output curves discussed above, does not tell one exactly what the venous return will be, but tells instead what the venous return would be if the right atrial pressure were known. Furthermore, this venous return curve depicts the circulatory conditions at a given instant, but it can become considerably altered, as will be discussed below, from one instant to another. For this reason, all the different points along the curve must be measured under identical circulatory conditions. This has been difficult to do, because any time the venous return falls to subnormal values, circulatory reflexes immediately ensue, attempting to return the venous return back toward a normal value. In so doing, the venous return curve becomes greatly altered, which also will be discussed below. To prevent this, two different methods have been used to measure the venous return curve without altering systemic conditions by circulatory reflexes or by other circulatory changes during the course of measurement. First, venous return curves have been measured in animals subjected to total spinal anesthesia, which abrogates all circulatory reflexes. However, to determine the normal venous return curve, a drip of epinephrine or norepinephrine is administered to the animal to return the vasomotor tone back to normal prior to making the measurements necessary to establish the curve.

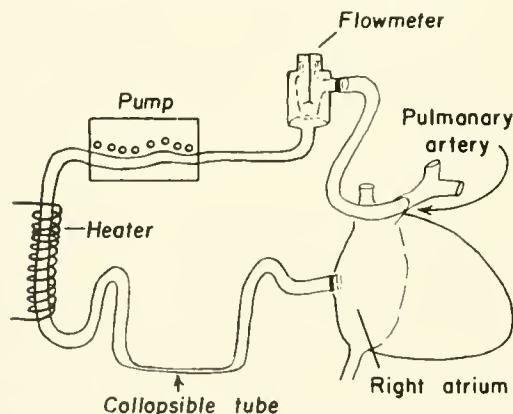


FIG. 4. External perfusion system in which a pump controls the activity of the heart. Using this external system it is possible to raise and lower the right atrial pressure at will while studying the effect of right atrial pressure on venous return.

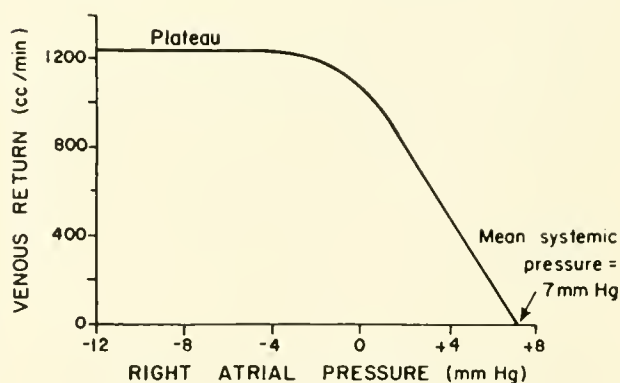


FIG. 5. The normal venous return curve.

The second method for establishing the normal venous return curve has been to determine different points along the curve intermittently by suddenly elevating the right atrial pressure and making venous return measurements within the next 5 to 7 sec before circulatory reflexes can take place. Then the circulation is returned to normal, and after a reasonable control period another intermittent measurement is made.

The venous return curves recorded by these two different procedures have been identical. Furthermore, venous return curves have been recorded in closed-chest animals in which a special occluding system has been surgically placed around the pulmonary artery so that the pulmonary artery could be occluded to any desired degree (97). Then, using especially the intermittent procedure, points along the venous return curve were established. The results agree with the measurements established when using the above two procedures.

The venous return curve of figure 5 is the average curve, recorded in approximately 100 separate dogs anesthetized with sodium pentobarbital, and then extrapolated on a weight basis to the 12-kg dog. Several features of this curve deserve special comment.

First, when the right atrial pressure becomes more negative than 0 to -4 mm Hg, a further increase in the negativity of the right atrial pressure does not cause a further increase in venous return. In other words, the venous return curve reaches a "plateau." The cause of this effect is the well-known collapse factor in veins (88, 112). One can actually see the veins entering the thoracic cavity begin to collapse when the right atrial pressure becomes negative with respect to atmospheric pressure. Furthermore, measurements in the veins immediately beyond the collapsed points show that these veins all have approximately 0 mm Hg pressure in them regardless of how low the right atrial pressure falls. Thus, the collapse factor effectively sets the venous pressure of the blood leaving the systemic circulation almost exactly at 0.

The second important point in relation to the venous return curve is that elevation of the right atrial pressure above 0 causes a very rapid decrease in return of blood from the systemic circulation (98). On the average, for each mm Hg rise in pressure above 0, the venous return decreases 14 per cent, and it reaches zero when the right atrial pressure has risen to approximately $+7$ mm Hg in "areflex" dogs.

The third important point is that when venous return reaches zero, the right atrial pressure at this

level is equal to the mean systemic pressure (98). The mean systemic pressure is the pressure in the systemic circulation that is measured if the root of the aorta and the large systemic veins entering the heart are suddenly occluded and all pressures in the systemic circulation are brought instantaneously to equilibrium. That is, when blood flow ceases absolutely in the systemic circulation, the pressures in all its segments become equal. Therefore, the right atrial pressure becomes equal to the pressure everywhere in the systemic vessels. This equilibrium pressure is the mean systemic pressure.

The fourth point of major significance in relation to the venous return curve is the almost complete linearity of the venous return curve in the range between 0 right atrial pressure and the mean systemic pressure level. That is, the venous return is approximately proportional to the difference between mean systemic pressure and right atrial pressure ($P_{ms} - P_{ra}$). This difference is called the "pressure gradient for venous return" (81), and it is an important concept in establishing the forces that lead to the flow of blood toward the heart. This will be seen below, especially in relation to alterations in systemic resistances, for when there is no pressure gradient for venous return, there will be no venous return to the heart regardless of the changes in systemic resistances.

EFFECT OF PERIPHERAL RESISTANCE ON VENOUS RETURN. Figure 6 illustrates the effect on the venous return

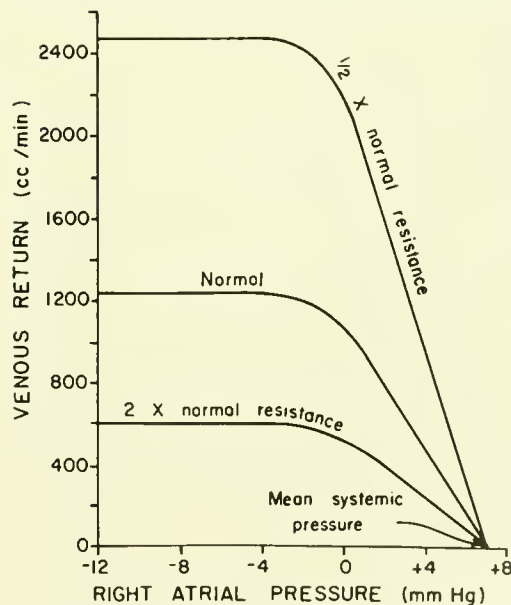


FIG. 6. Effect on the venous return curve of changing the peripheral resistance. Note that the mean systemic pressure remains constant at approximately 7 mm Hg.

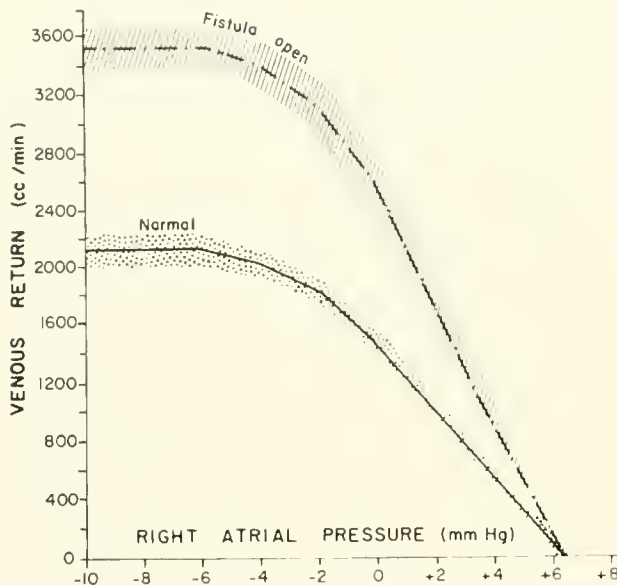


FIG. 7. Effect on the venous return curve of suddenly opening large bilateral femoral A-V fistulae.

curve of changing the systemic resistance from normal (87). Note that the venous return is exactly zero in the case of each of these three curves when the right atrial pressure is equal to the mean systemic pressure. That is, when there is no pressure gradient for venous return, there is likewise no flow toward the heart. Yet, when the right atrial pressure falls to some value below the mean systemic pressure, then a pressure gradient does exist for forcing blood toward the heart, and the return of blood is inversely proportional to the resistance. The greater the resistance, the less is the return of blood to the heart, and the less the resistance, the greater is the venous return. Thus, figure 6 shows the normal venous return curve, a venous return curve in which the resistances throughout the systemic circulation are approximately one-half normal, and a venous return curve in which the resistances are approximately two times normal.

Figure 7 illustrates a typical experiment in which peripheral resistance was suddenly changed while all other conditions of the circulation were kept as nearly constant as possible (103). In this instance two large femoral A-V fistulae were suddenly opened so that the total peripheral resistance was decreased to approximately 60 per cent of the control value. Circulatory pressures remained exactly constant. Note that the study depicts precisely the same effects as those illustrated in the previous figure but this time showing a typical and actual experimental study

It should not be supposed, however, that increasing the resistance to blood flow in the arteries affects venous return equally as much as increasing the resistance in the veins. Indeed, for a given increase in venous resistance, the venous return decreases approximately eight times as much as when the arterial resistance is increased the same amount. This was illustrated by a comparative study in which arterial resistance was increased by injecting microspheres into the arterial system and venous resistance was increased by progressive occlusion of all the large veins emptying into the right atrium (87). Figure 8 illustrates the difference between these two effects, the upper curve showing that the total peripheral resistance could be increased by arterial embolization to as much as 400 to 500 per cent of control values before the venous return decreased a great amount. On the other hand, increasing the total peripheral resistance only 30 per cent by the method of venous compression decreased the venous return to one-half normal.

The cause of this difference between venous resistance and arterial resistance is that the arterial system proximal to the arterioles has very little capacitance (DV/DP) in relation to the total capacitance of the systemic circulation proximal to the venous constriction at the outflow of the veins into the heart (89). Because of the small storage ability of the arteries for blood, increasing the resistance at the arterioles elevates the arterial pressure almost as

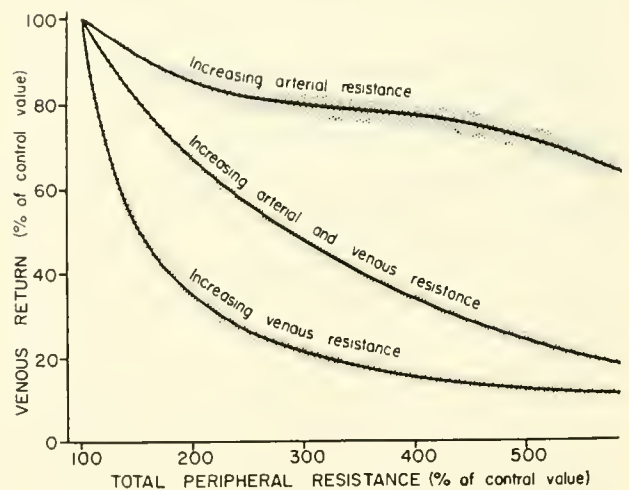


FIG. 8. Effect on venous return of increasing the total peripheral resistance when the resistance is increased in three different ways: 1) by injecting microspheres into the arteries to increase arterial resistance, 2) by constricting the inflow veins to the heart, and 3) by a combination of these two procedures. [From Guyton *et al.* (87).]

much as the resistance rises, and the arterial pressure then simply forces the blood on past the resistance. On the other hand, constricting the veins where they empty into the heart causes the pressure in the veins to rise only a few mm Hg because of the great storage capacity of the veins. This small rise in venous pressure is far too little to overcome the increasing resistance, and, as a consequence, the venous return becomes tremendously depressed. Therefore, venous resistance affects venous return to the heart many times as much as arteriolar or arterial resistance of the same magnitude.

EFFECT OF MEAN SYSTEMIC PRESSURE ON VENOUS RETURN. Basically the mean systemic pressure is the resultant of the ratio of *a*) the blood volume to *b*) the ability of the circulatory system to hold blood. As the blood volume increases, the mean systemic pressure remains essentially zero until the blood barely begins to distend the blood vessels. But, once this point has passed, any further increase in blood volume increases the mean systemic pressure directly in proportion to the additional amount of blood injected into the circulation, the mean systemic pressure rising approximately 1 mm Hg for each 2 per cent increase in blood volume (86). Thus, it can be seen that very small changes in blood volume can cause relatively large changes in mean systemic pressure and, as a consequence, can have a marked effect on venous return unless other circulatory compensations prevent this.

Only a few measurements of mean systemic pressure have ever been made, for this requires instantaneous stoppage of the circulation and then rapid equilibration of the pressures in all segments of the systemic circulation before any blood can leave or before circulatory reflexes or other factors can change the vascular distensibility. In our laboratory, we have measured this pressure a few times by suddenly constricting the aorta and pulmonary arteries (138), utilizing devices implanted several weeks previously in the thoracic cavity to cause the constrictions. These pressure measurements showed a normal mean systemic pressure of almost exactly 7 mm Hg.

Far more measurements have been made of the mean circulatory pressure (101, 105, 180, 182) than of the mean systemic pressure; approximately 1000 such measurements have been made in our laboratory. Since the mean systemic pressure is of such extreme importance in determining venous return to the heart, the few measurements of mean systemic pressure have been compared with measurements of

mean circulatory pressure. In all instances, the mean systemic pressure has been almost identical with the mean circulatory pressure except in the case of extreme engorgement of the pulmonary circulation, and even here the difference has been only 1 mm Hg or so. Therefore, insofar as venous return from the systemic circulation is concerned, one can consider the mean systemic pressure and mean circulatory pressure to be almost identical.

Measurements of mean circulatory pressure can be made very easily by electrically fibrillating the heart with 60-cycle current applied to needle electrodes in the anterior chest wall at approximately 50 v. Studies have demonstrated that all pressures of significance in the measurement of mean circulatory pressure come to equilibrium within only a few seconds after cardiac fibrillation begins, except for the pressures of the systemic arterial chamber and the systemic venous chamber. Therefore, immediately after fibrillation of the heart begins, arterial blood is pumped from a catheter lying in the descending aorta and thence through another catheter into the inferior vena cava. After only 3 to 5 sec, the pressures in these two chambers are brought to equilibrium and the mean circulatory pressure measured. During the next few seconds the heart is defibrillated by passing 4 to 10 amperes of 60-cycle alternating current at 440 v for $\frac{1}{10}$ sec directly through the chest anteroposteriorly (104). After 2 to 3 min of recovery, the animal returns to essentially normal circulatory conditions.

Figure 9 illustrates the typical effect on the venous

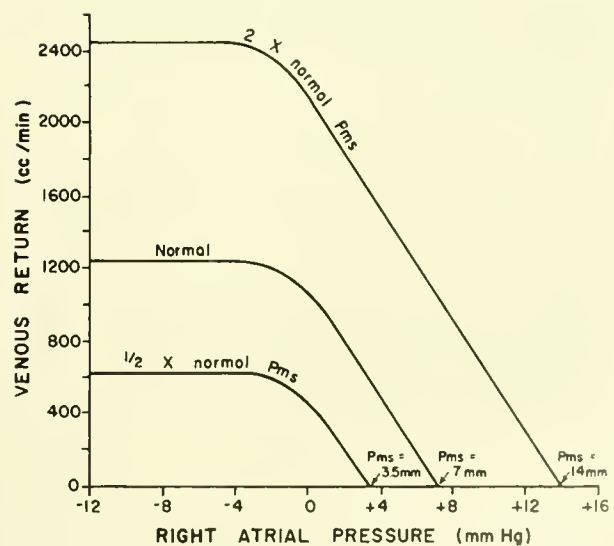


FIG. 9. Effect on the venous return curve caused by changes in mean systemic pressure.

return curve caused by altering the mean systemic pressure. Note that when the mean systemic pressure is increased from the normal value of 7 mm Hg up to 14 mm Hg the curve is shifted to the right and its plateau becomes approximately twice as high as normal. Conversely, when the mean systemic pressure is decreased to 3.5 mm Hg, which is one-half normal, the curve is shifted to the left, and the plateau becomes reduced to one-half normal. Since the flow of blood to the heart is proportional to the pressure gradient for venous return, which in turn is equal to the mean systemic pressure minus the right atrial pressure, one can see that any increase in mean systemic pressure causes a corresponding increase in venous return at any given right atrial pressure. Likewise, any decrease in the mean systemic pressure will cause a corresponding decrease in venous return at all right atrial pressures.

Figure 10 depicts venous return curves in a series of normal dogs and then again in the same dogs after an average infusion of 200 ml of blood and also after hemorrhage of 122 ml (99). Note that the normal mean systemic pressure was approximately 7.7 mm Hg, that this rose to 11.3 mm Hg in the infused dog, and that it fell to 4.7 mm Hg in the hemorrhaged dog. This experiment illustrates typical shift of the venous return curves to the right as the blood volume increases, thereby increasing the mean systemic pressure.

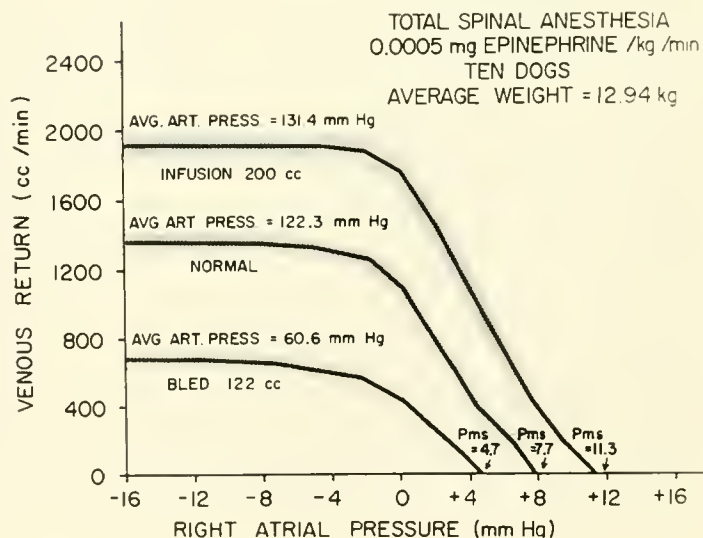
Changes in the distensibility of the vascular system or changes in the pressure on the outside of the vessels can alter the mean circulatory pressure in exactly the same manner as can alterations in blood volume. These changes include *a*) increased vaso-

motor tone, caused either by sympathetic stimulation or by infusion of sympathomimetic drugs; *b*) pressure on the abdomen, which compresses large intra-abdominal blood reservoirs; *c*) increased intrathoracic pressure, which compresses the blood reservoirs of the chest; and *d*) increased interstitial fluid volume, which causes pressure on the outside of blood vessels throughout the body. In normal circulatory adjustments the most important of these is the effect of vasomotor tone on the mean systemic pressure.

Figure 11 illustrates the average results from 11 typical experiments in dogs in which the degree of vasomotor tone was altered from the minimal level up to almost the maximal level (95). This shows the typical effects one would expect when the mean systemic pressure is elevated, that is, progressive shift of the venous return curves to the right as the vasomotor tone is increased.

One might have expected the administration of a sympathomimetic drug to cause increased resistance to blood flow toward the heart as well as to increase the mean circulatory pressure. This was not evident from these studies, for the venous return curves did not decrease in slope as the rate of epinephrine injection was increased. On second thought, one can understand why this was true. When vasomotor tone is increased throughout the circulation while the blood volume remains constant, pressures everywhere in the circulation will tend to rise because of tightening of the vessels around the blood. But, if any single segment of the circulation constricts, some other segment of the circulation must dilate. On the average, then, for every constriction that occurs in the systemic circulation following the injection of

FIG. 10. Effect of increasing or decreasing the blood volume on the venous return curves. Total spinal anesthesia was instituted to prevent cardiovascular reflexes during the course of the experiment. [From Guyton *et al.* (99).]



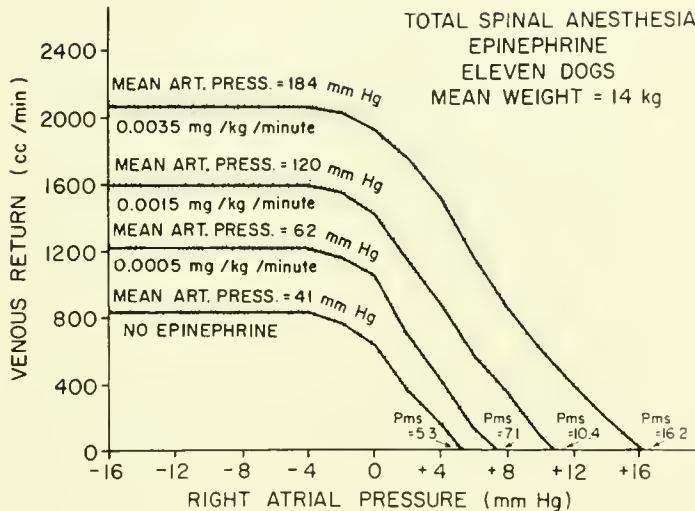


FIG. 11. Effect of different rates of epinephrine injection on the venous return curves. Note that the principal effect is to increase the mean systemic pressure. [From Guyton *et al.* (95).]

epinephrine, as depicted in the experiments of figure 11, there had to be equal dilatation somewhere else. Indeed, measurements have shown that, as the arterioles constrict under these conditions, there is a tendency for the veins to dilate even though the walls of the veins do tighten to a very great extent (55). This elevates the mean systemic pressure but does not increase the resistance to blood flow from the systemic vessels toward the heart. In essence, then, we can say that an increase in vasomotor tone affects venous return principally by increasing the mean systemic pressure, and, usually, an increase in vasomotor tone does not increase the average resistance that opposes the return of blood to the heart.

SUMMARY OF FACTORS THAT AFFECT THE VENOUS RETURN CURVES. Basically, there are only two different patterns of changes in venous return curves, those that result from *a*) changes in resistance in the systemic circulation, and *b*) changes in the mean systemic pressure. Figure 6 depicts the pattern of venous return curves that results from alteration of vascular resistance, while figure 9 illustrates the curves that result from alteration of mean systemic pressure.

Any factor that alters resistance, whether this be a localized or generalized alteration, will correspondingly alter the venous return curve. However, alteration of the venous resistance affects venous return far more drastically than alteration of the arterial resistance.

The factors that affect the mean systemic pressure can be divided into two main groups: 1) those that affect the blood volume, and 2) those that affect the ability of the circulatory system to hold blood. The two most important factors of all that affect mean

systemic pressure are blood volume itself and changes in vasomotor tone.

The interrelationships of all these different factors on the return of blood to the heart can be expressed mathematically by the following formula (98):

$$VR = \frac{P_{ms} - P_{ra}}{\frac{R_v C_v + (R_v + R_a) C_a}{C_v + C_a}}$$

In this formula VR is venous return, P_{ms} is mean systemic pressure, P_{ra} is right atrial pressure, C_v is capacitance of the veins, C_a is capacitance of the arterial tree, R_v is the average resistance to blood flow from the veins to the heart, and R_a is the resistance from the arterial tree to the venous tree. This formula shows that venous return is approximately proportional to the mean systemic pressure minus right atrial pressure, which has been called the "pressure gradient for venous return," while, on the other hand, venous return is inversely proportional to the resistances in the systemic circulation. The capacitances in the formula are constants for any given animal, and they determine the relative importance of arterial resistance versus venous resistance. In the normal animal a given change in venous outflow resistance affects venous return approximately eight times as much as the same change in arterial resistance (87).

Equating the Venous Return and Cardiac Output Curves

If one understands the different factors that affect venous return and cardiac output curves, he can readily determine the approximate effects of any given circulatory change on each of these two types

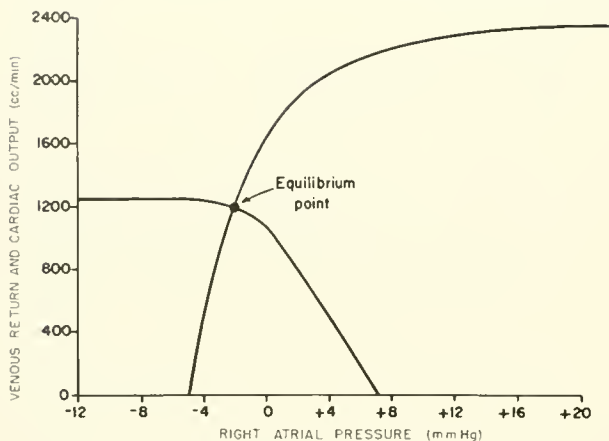


FIG. 12. Equating of a normal cardiac output curve and a normal venous return curve for a 12-kg dog.

of curves. Then by plotting the two curves on the same coordinates, as shown in figure 12, the equations represented by the separate curves can be solved (81). Figure 12 illustrates the equating of a normal venous return curve with a normal cardiac output curve, as depicted for the 10-kg dog. Note that there is only one single point at which the flows and the pressures for the two curves are equal, and this point is called the "equilibrium point." It represents the solution to our graphical analysis, depicting in figure 12 that this particular dog at this particular time has a cardiac output of 1200 ml per min, a venous return also of 1200 ml per min, and a right atrial pressure of -2 mm Hg (referred to the level of the tricuspid valve).

Looking once again at figure 12, let us assume that an extra quantity of 25 ml of blood is suddenly injected into the right atrium. This would raise the right atrial pressure to approximately $+4$ mm Hg, and, as depicted by the venous return curve, the elevated right atrial pressure would decrease the venous return to approximately 500 ml per min. On the other hand, the high right atrial pressure would cause the cardiac output, as depicted by the cardiac output curve, to rise to approximately 2000 ml per min. Thus, a disparity of 1500 ml per min develops between venous return and cardiac output so that far more blood is pumped out of the heart than returns to it. Therefore, within the next three to six heartbeats, the right atrial pressure falls back to the level of -2 , thus causing the venous return to rise up to 1200 ml and the cardiac output to fall to 1200 ml. In other words, within a few seconds, equilibrium will be re-established whenever venous return and cardiac output deviate from each other (35).

EFFECT OF SYMPATHETIC STIMULATION ON VENOUS RETURN, CARDIAC OUTPUT, AND RIGHT ATRIAL PRESSURE. Using the same principles for equating venous return and cardiac output curves as depicted in figure 12, we can now show in figure 13 the effect of strong sympathetic stimulation on venous return, cardiac output, and right atrial pressure. The dashed curves of the figure illustrate the normal curves. Then, suddenly, sympathetic stimulation changes both the venous return and cardiac output curves to the respective solid curves (95). Note that the venous return curve shifts far to the right and upward because of an increase in "mean systemic pressure," and the cardiac output curve shifts upward, as is characteristic of a hypereffective heart. These two curves equate at an entirely new point, the new equilibrium point occurring at a right atrial pressure of -3 mm Hg and a cardiac output and venous return of 1800 ml per min.

This analysis of the effects of sympathetic stimulation agrees with the typical experimental result found when the sympathetics are stimulated throughout the body, that is, a mild to moderate increase in venous return and cardiac output and usually a slight decrease in right atrial pressure (169). Almost

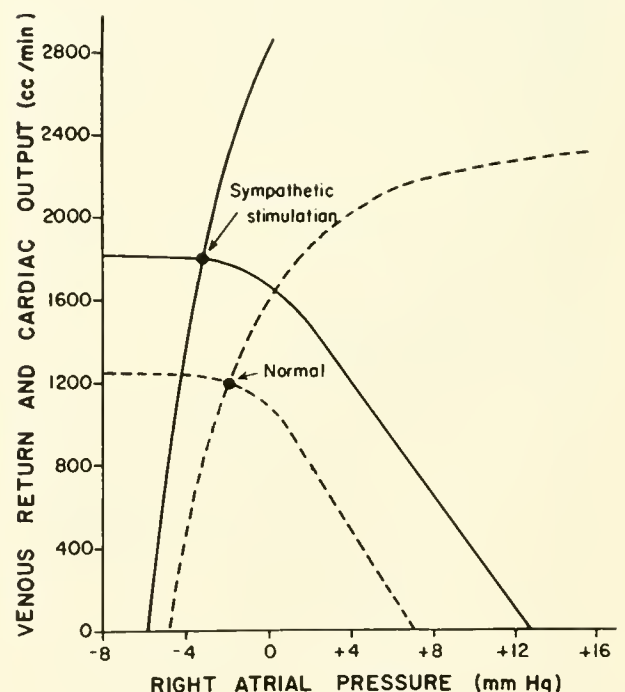


FIG. 13. Effect of sympathetic stimulation on the venous return and cardiac output curves, showing an increase in cardiac output and venous return and a decrease in right atrial pressure.

exactly the opposite effects occur when vasomotor tone is greatly reduced throughout the body by the administration of nitrites (195) or ganglion-blocking agents (189). Likewise, pooling of blood in the lower part of the body when one stands (5, 76, 142-144, 175, 184, 196) or sequestration of blood in the limbs by the application of tourniquets (59, 193) reduces the venous return and cardiac output in a closely similar manner.

EFFECT OF MUSCULAR EXERCISE ON VENOUS RETURN, CARDIAC OUTPUT, AND RIGHT ATRIAL PRESSURE. Figure 14 illustrates an analysis of the circulation during exercise, showing changes in both the cardiac output and venous return curves. The cardiac output curve is elevated as a result of *a*) sympathetic stimulation of the heart, and *b*) inhibition of the vagi to the heart, thus giving a cardiac output curve of a hypereffective heart.

Three different factors cause the observed alterations in the venous return curve. First, tightening of the musculature throughout the body, particularly

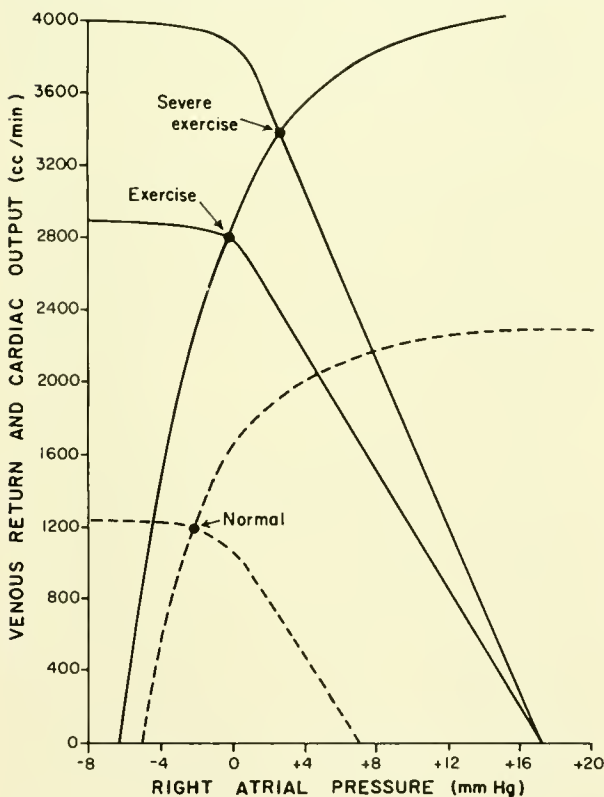


FIG. 14. Effect of exercise on the venous return and cardiac output curves, showing that the new curves equate at greatly elevated venous returns and cardiac outputs. Also, the right atrial pressures are still close to zero mm Hg.

tightening of the abdominal musculature, causes an instantaneous increase in mean systemic pressure of several millimeters of mercury (100). Second, sympathetic stimulation causes considerable increase in mean systemic pressure (101). Third, the blood vessels of the musculature are likely to become markedly dilated, thus decreasing the resistance to blood flow through the systemic circulation (12); this, in turn, increases the slope of the venous return curve (87). Thus, we find that in moderate exercise the cardiac output and venous return may be increased to two or more times normal, and the right atrial pressure will still be only slightly elevated (14, 169, 174). On the other hand, in severe exercise, the heart is then often taxed to its limit so that the right atrial pressure rises considerably as depicted by the highest equilibrium point in the figure. In an animal or human being that has been thoroughly trained for athletics, the cardiac output curve of the heart can rise to one and one-half to two times that depicted in figure 13, thus giving as much as a five- to sevenfold increase in cardiac output without an elevation of right atrial pressure above zero.

Here, again, it is quite evident that simultaneous analysis of the function of the heart and of peripheral circulatory factors is needed to ascertain the integrated effects of exercise on venous return, cardiac output, and right atrial pressure (10, 39, 50, 169, 177, 188).

EFFECT OF RAPID TRANSFUSION ON VENOUS RETURN, CARDIAC OUTPUT, AND RIGHT ATRIAL PRESSURE. Figure 15 depicts the effects of rapidly infusing an animal with whole blood. The immediate effect stems mainly from an increase in mean systemic pressure (99)—in this instance from 7 mm Hg to 11.5 mm Hg. However, the increased blood volume also distends the vessels of the systemic circulation, thus decreasing the peripheral resistance and therefore increasing the "slope" of the venous return curve. In the case of the heart, circulatory reflexes, especially the pressoreceptor reflex, actually weaken the heart because the excess blood volume tends to elevate arterial pressure, thereby initiating inverse reflexes. As a consequence, the cardiac output curve decreases very slightly. The net result, as depicted by the equilibrium point, is a moderate increase in venous return and cardiac output and a very marked rise in right atrial pressure, which are effects that have been observed many times by many different investigators (66-69, 115, 183). This figure and the previous one illustrates that the relationship between right atrial

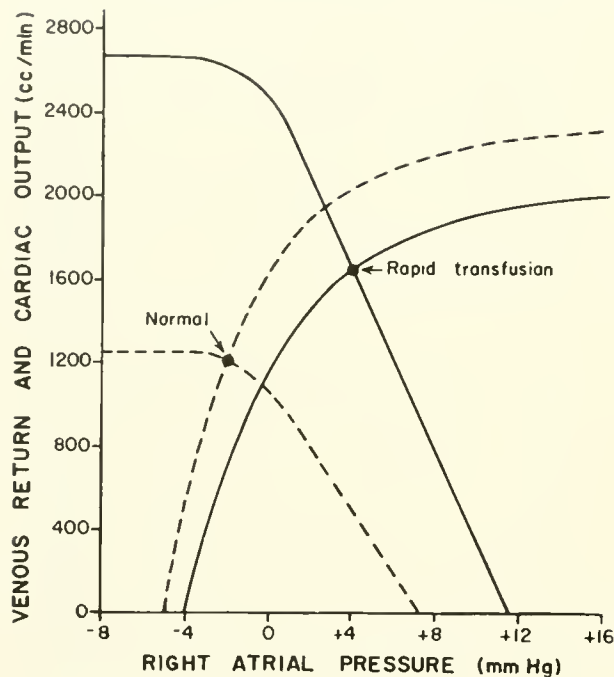


FIG. 15. Effect of rapid transfusion of blood on venous return and cardiac output curves, showing the result to be an elevated venous return and cardiac output and also a considerably elevated right atrial pressure.

pressure and cardiac output is not always even directionally the same (169), for in some circulatory conditions the cardiac output rises while the right atrial pressure falls; at other times, as in figure 15, the right atrial pressure can rise very greatly while the venous return and cardiac output change relatively little.

EFFECT OF SHOCK ON VENOUS RETURN, CARDIAC OUTPUT, AND RIGHT ATRIAL PRESSURE. Figure 16 depicts by the dashed curves the normal equating of venous return and cardiac output curves and then by the solid curves the effects immediately after hemorrhage in the so-called compensated stage of shock. In this instance, the hemorrhage has reduced the mean systemic pressure considerably, shifting the venous return curve to the left (99). Immediately, however, circulatory reflexes have become active, causing the heart to become hypereffective and greatly elevating the cardiac output curve. The decreased blood volume also causes the slope of the venous return curve to decrease. Therefore, for two reasons, 1) decreased mean systemic pressure, and 2) increased resistance to venous return, the venous return curve is shifted to the left, and its plateau is reduced. Therefore, the venous return and the cardiac output curves equate

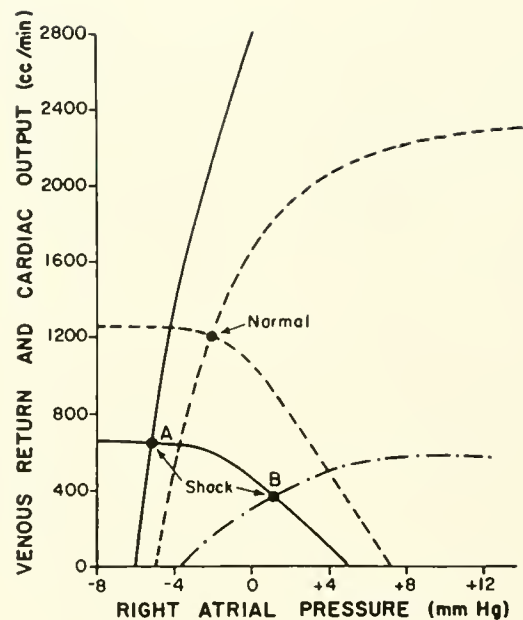


FIG. 16. Effect of shock on the venous return and cardiac output curves, showing in the early compensated stage of shock a low venous return and cardiac output but also a greatly depressed right atrial pressure (point A). In irreversible shock the cardiac output becomes greatly depressed as illustrated by the dash-dot curve; venous return and cardiac output become greatly reduced while the right atrial pressure rises (point B).

at point A, the cardiac output and venous return falling to about one-half normal and the right atrial pressure falling to -5 mm Hg. These are typical effects observed following acute hemorrhage (90, 160, 161, 167). Very similar effects occur in persons with vasomotor collapse except that the partial reflex compensation which occurs following hemorrhage is absent (147).

In the irreversible stage of shock an entirely different situation ensues, because the heart then begins to deteriorate. This has been shown especially by the work of Crowell (92), but also by measurements made in Wiggers' laboratory (61, 150, 197, 198) and by Remington (161). The cardiac output curve falls to the lower curve of the figure, and the new equilibrium point is now point B. Thus, the venous return and cardiac output fall to a still lower value while the right atrial pressure begins to rise; these are typical events in the irreversible and terminal stage of shock. As a result of this additional decrease in cardiac output, the heart deteriorates still more, and a vicious cycle of cardiac deterioration develops, causing a progressive rise in right atrial pressure and a progressive fall in venous return and cardiac output.

EFFECT OF OPENING THE CHEST ON VENOUS RETURN, CARDIAC OUTPUT, AND RIGHT ATRIAL PRESSURE. Figure 17 illustrates the changes that occur in the circulation when the chest is opened. The dashed curves represent the normal circulatory conditions and then the long dashed curve represents the immediate effects on the cardiac output curve caused by opening the chest. The new equilibrium point, point *A*, shows that the cardiac output falls to approximately two-thirds normal and the right atrial pressure rises immediately from -2 mm Hg to $+2$ mm Hg. However, within approximately 30 sec to 1 min, circulatory reflexes, especially pressoreceptor reflexes, cause *a*) the cardiac output curve to rise to that depicted by the solid curve, and *b*) the venous return curve to shift to the solid venous return curve. These two curves equate at point *B* which depicts the final effects of opening the chest on cardiac output, that is, only a little decrease in cardiac output (22) but a considerable rise in right atrial pressure. One might immediately ask, therefore: Does opening the chest have any significant detrimental effect on the circulation? The answer to this is very definitely "yes", for the following reasons: In order for the venous return and cardiac output to recompensate essentially to normal, strong circulatory reflexes will have been set into play. Thus, an animal with his chest open has already utilized a major share of his circulatory reflex power simply to compensate for opening the chest. Now, the reserve reflex power left to compen-

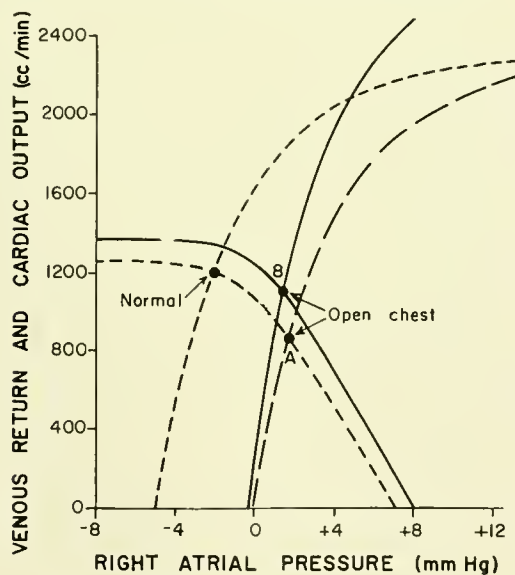


FIG. 17. Effect of opening the chest on the venous return and cardiac output curves, showing by point *A* the immediate effect and point *B* the effect after circulatory reflexes ensue.

sate for other circulatory stresses, such as hemorrhage, has been greatly reduced. Therefore, it can be said that the "circulatory reserve" has been considerably reduced as a result of the opened chest. This analysis, therefore, explains why the cardiac outputs of open-chest animals are normally only slightly below those of normal animals, but it also explains why animals and human beings under these conditions can withstand far less circulatory stress than can the normal (42).

EFFECT OF MYOCARDIAL DAMAGE ON VENOUS RETURN, CARDIAC OUTPUT, AND RIGHT ATRIAL PRESSURE. Figure 18 illustrates the progressive changes that occur in the circulation following sudden acute myocardial damage to both sides of the heart approximately equally. The short dashed curves illustrate normal equilibrium conditions. Then, suddenly, the heart becomes severely damaged as a result of acute myocardial infarction, reducing the cardiac output curve to that depicted by the long dashes. As a result, the new equilibrium point is now approximately one-third normal, and the right atrial pressure has risen to $+4$ mm Hg. However, these conditions do not obtain for a prolonged period of time because autonomic reflexes, mainly sympathetic, cause immediate compensations within the next 30 sec to 2 min (2-4, 40, 80, 152). At the end of this period, the sympathetic stimulation will have increased the cardiac output

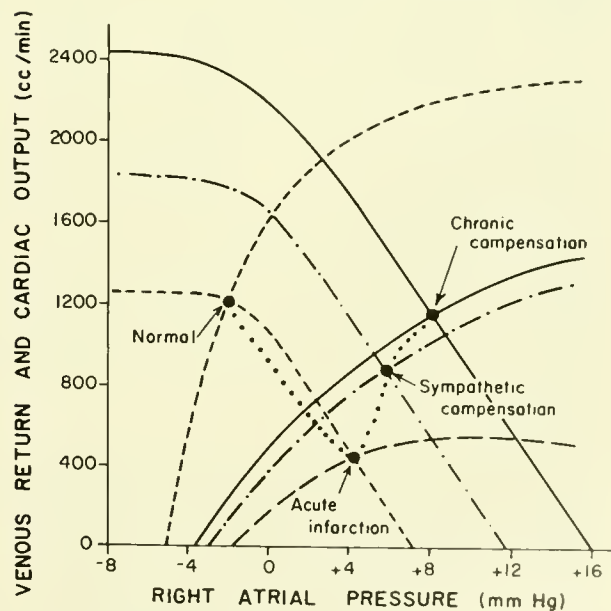


FIG. 18. Effect of acute myocardial infarction and subsequent stages of recovery on the cardiac output and venous return curves. The sequence of events is explained in the text.

and venous return curves up to those depicted by the dashes and dots. Therefore, within 2 min, the venous return and cardiac output will have returned to approximately two-thirds normal, and the right atrial pressure will have risen another 2 mm Hg up to +6 mm Hg. But, even this is an abnormally low cardiac output which is still insufficient to supply all the tissues of the body with adequate amounts of blood. Furthermore, there is intense sympathetic vasoconstriction throughout the circulatory system during this period of time as well as sometimes a decreased arterial pressure; the intense sympathetic vasoconstriction (134) and the decreased arterial pressure (135) both decrease renal output. Furthermore, the semishock state that exists at this stage causes the adrenal glands to secrete large quantities of aldosterone. This, in turn, promotes rapid reabsorption of sodium from the renal tubules, associated also with rapid reabsorption of water (48). The net effect on the kidneys, therefore, is to reduce renal output greatly or, at times, even to stop renal output completely. Over a period of the next few days, fluid is progressively retained in the circulatory system, thus shifting the venous return curve in figure 18 further and further to the right (99, 105). The solid venous return curve depicts approximately that which will obtain after a week or so of fluid retention.

Simultaneously with the changes that take place in the venous return curve, the heart will also be changing. If the infarction is an uncomplicated one and recovery from the infarction begins immediately, then the cardiac output curve of figure 18 will progressively rise. The solid cardiac output curve depicts approximately that which one would expect after a week of recovery. As illustrated by the point at which the solid cardiac output curve equates with the solid venous return curve, we find that the cardiac output and venous return will have now returned almost completely to normal but that the right atrial pressure again will have risen another 2 mm Hg. This is characteristic of the chronic stage of congestive heart failure, that is, the cardiac output may be normal or slightly below normal, but the venous pressures are essentially always greatly elevated.

Another effect that occurs as the cardiac output approaches normal is that the degree of sympathetic activity throughout the body also gradually becomes reduced toward normal. Furthermore, the body is no longer in a shocklike state so that the output of aldosterone also becomes reduced. As a consequence, renal output once again returns toward normal, thus preventing further retention of fluid. Therefore, the circulatory system has now reached a new steady

state, with the cardiac output and venous return essentially normal, renal output once again essentially normal, but the right atrial pressure considerably elevated.

It should be noted again that the analysis illustrated in figure 18 is that for myocardial damage affecting both ventricles approximately equally. The course of events depicted by the dotted line is typical of that normally observed following acute generalized myocardial infarction (13, 71, 73, 75, 106-108, 121, 162, 163, 166). We shall see that the more complicated graphical analysis presented later in the chapter is much more satisfactory than the simple graphical analysis when one side of the heart fails to a greater extent than the other side.

ANALYSIS OF DECOMPENSATION AND COMPENSATION IN CONGESTIVE HEART FAILURE. Figure 19 illustrates an analysis of decompensation in severe cardiac failure. This shows by the two dashed curves the analysis for the normal circulatory system in a normal 10-kg dog. Then, at the bottom of the graph, it shows the typical cardiac output curve for a severely damaged heart after all sympathetic reflexes and all recovery that are possible have taken place (38). If we assume that the cardiac output curve suddenly falls from the normal down to this depressed curve, then we find that the cardiac output immediately falls to point *A*, about two-fifths normal, with a right atrial pressure of approximately +4 mm Hg. This cardiac output is far too little to cause normal renal function, and, for the same reasons discussed above, renal output becomes severely depressed. As a result, fluids are retained in the body, and the mean systemic pressure progressively rises, shifting the venous return curves to the right and progressively elevating their plateaus. Thus, during the ensuing days, with the progressive retention of fluid, the equilibrium points in figure 19 proceed to *B*, *C*, *D*, *E*, *F*, and *G*. It is especially interesting that cardiac output curves of severely damaged hearts do not rise to a plateau but, instead, rise to a peak and then begin to descend (117). Therefore, after the process of decompensation has proceeded past the peak at point *E*, further retention of fluid causes a reduction in cardiac output rather than an increase.

The significant factor in decompensation is that even at its greatest peak, the cardiac output curve never reaches the necessary cardiac output level required to re-establish normal renal function. Consequently, fluids continue to be retained indefinitely until death of the animal.

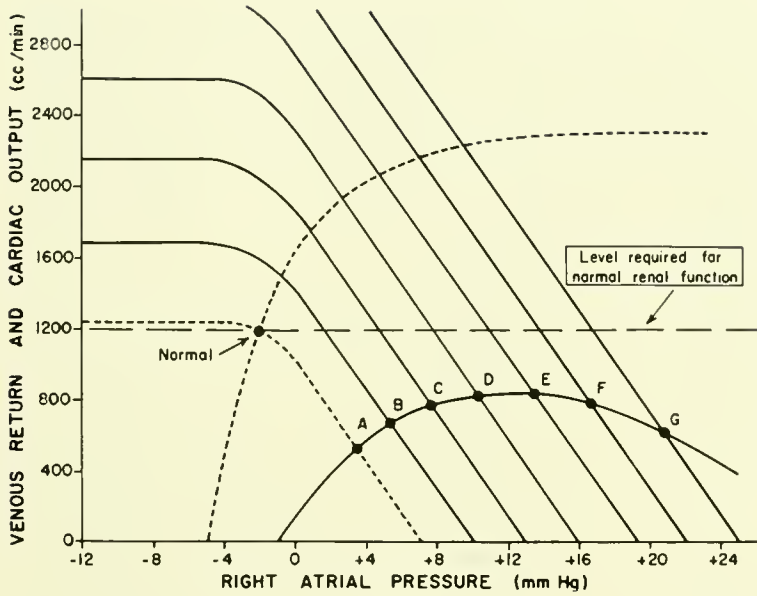


FIG. 19. Analysis of decompensated heart disease, showing a greatly depressed cardiac output curve and a progressive shift of the venous return curves to the right until death occurs, as explained in the text.

Figure 20 depicts recompensation of the animal that had been almost dead from decompensated heart disease. The lower curve illustrates a cardiac output curve of a decompensated heart, showing that after a period of time the venous return curve had already reached the far right curve with equilibrium occurring at point A. Then, upon instituting appropriate treatment, such as the administration of digitalis (117), the heart becomes considerably stronger, and the cardiac output curve rises to the upper curve. If this rise is relatively rapid, the venous return curve will not be immediately affected. Therefore, the new equilibrium point becomes point B, which represents a cardiac output greater than that required for normal renal function. As a consequence, the output of urine now becomes actually far greater than normal, which is a well-known effect of digitalis when a decompensated state is converted into a compensated state. The output of urine causes a decrease in mean circulatory pressure and a progressive shift in the venous return curves toward the left. Thus, during the ensuing days, the equilibrium points in figure 20 shift from point B to C, to D, and finally E. At point E the venous return curve becomes stable because now the cardiac output has fallen back to a value that is just sufficient to maintain a renal output equal to the daily intake of fluid and salts. One can see that we now have three different curves equating with each other, the cardiac output curve, the venous return curve, and a straight line which is a curve representing the level required for normal renal function. It is where these three

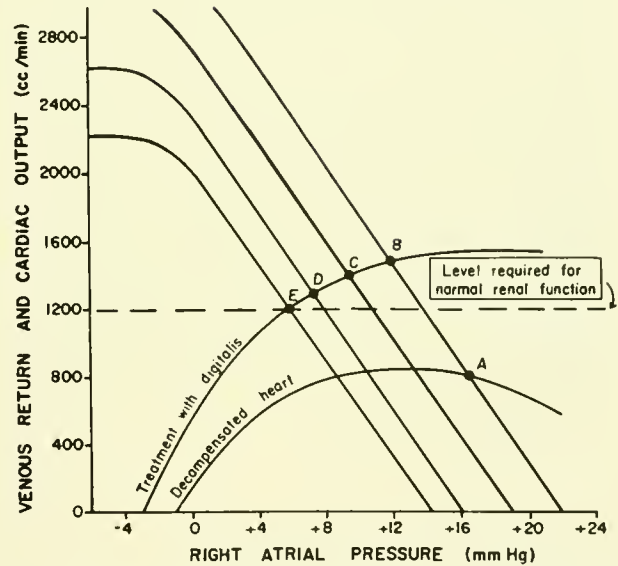


FIG. 20. Analysis of recompensation after a bout of cardiac decompensation. The lower cardiac output curve represents the decompensated heart and the upper curve the recompensated heart. The sequence of events is explained in the text.

curves equate that the circulatory system finally establishes its steady-state equilibrium.

A heart can also be recompensated without increasing the cardiac output curve at all but simply by lowering the level required for normal function. For instance, in figure 20, if this were lowered down to a value of 700 ml per min, then point A would be approximately 100 ml per min greater than the level required for normal renal function. As a result fluid

would be lost and the venous return curves would proceed toward the left. This would continue until the cardiac output should fall to 700 ml per min, which would be the equilibrium point for the three different curves. The method by which this third curve, the level required for normal renal function, can be lowered is by administration of a diuretic or by drastic reduction of fluid and salt intake. Under either of these conditions the kidneys can then put out an amount of fluid equal to the daily intake despite the fact that the cardiac output is greatly reduced. Thus, the animal is kept from dying as a result of decompensation, and over a period of time its heart can perhaps recover or at least its life can be saved by continual adherence to a strict diuretic and fluid regimen.

ANALYSIS OF EFFECTS RESULTING FROM CHANGES IN VASCULAR RESISTANCE. The simplified graphical approach can also be used to analyze the effect of vascular resistance changes resulting from several different causes. For instance, the effects of anemia and polycythemia have been studied (102), and the results of the analyses are in accord with the experimental findings in these conditions (60, 109, 164, 176). Second, an analysis for A-V fistulae (104) also accords with the often repeated findings in these conditions (43, 116, 140, 148, 173). Third, a graphical analysis showing a very detrimental effect on venous return of increasing venous resistance (87) is in accord with many studies which have demonstrated that relatively slight venous constriction can cause either shock in the acute situation (63) or peripheral congestion in the chronic preparation (26).

A MORE COMPLEX GRAPHICAL ANALYSIS OF VENOUS RETURN, VENTRICULAR OUTPUTS, AND ATRIAL PRESSURES

The simplified graphical analysis which has just been presented is ordinarily quite satisfactory for analyzing the effects of most circulatory stresses on the circulation except when the stresses involve an imbalance between the left and right hearts. Such imbalances can result from unilateral cardiac failure or unilateral excess load on the heart. To determine the effects of these unilateral disturbances on the circulation, we now need to analyze the functions of all the four different segments illustrated in figure 1, all at the same time, that is, of the systemic circulation, the right heart, the pulmonary circulation, and the

left heart. Then all of these must be equated against each other. To do this we can proceed by pointing out, first, that the analyses of right heart venous return and right ventricular output are approximately the same as the analyses for the entire heart-lung segment. Therefore, right heart function, for practical purposes, can be depicted by the usual simplified analysis which has already been presented.

Also, the analyses for the pulmonary circulation and the left heart obey identically the same principles as those already discussed for the systemic circulation and right heart, though the quantitative values are entirely different. Figure 21 illustrates a typical analysis of venous return in the pulmonary circulation and also of the ventricular output of the left heart. Note that the left atrial pressure scale has been greatly shortened in relation to the right atrial pressure scale used in previous figures. The reason for this is that in later figures we will wish to use this analysis for the left heart in association with analyses for the right heart. When blood is shifted from the systemic circulation to the pulmonary circulation, the mean pulmonary pressure rises approximately 7 mm Hg for each 1 mm Hg fall in mean systemic pressure (138, 139, 146). Therefore, in the following equating procedures the scale for right atrial pressure will in all instances be seven times as great as the scale for left atrial pressure.

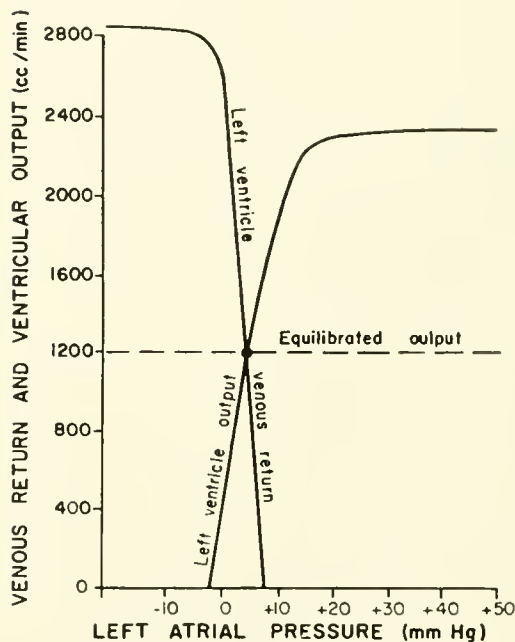


FIG. 21. Analysis of pulmonary venous return to the left heart and output from the left ventricle, illustrating the equating of these with each other in the steady-state condition.

In order to equate the events that take place in the left heart with those that take place in the right heart, we now need to transpose the direction of the scale for left atrial pressure. Figure 22 illustrates this transposition, showing now the left atrial pressure rising from right to left rather than from left to right.

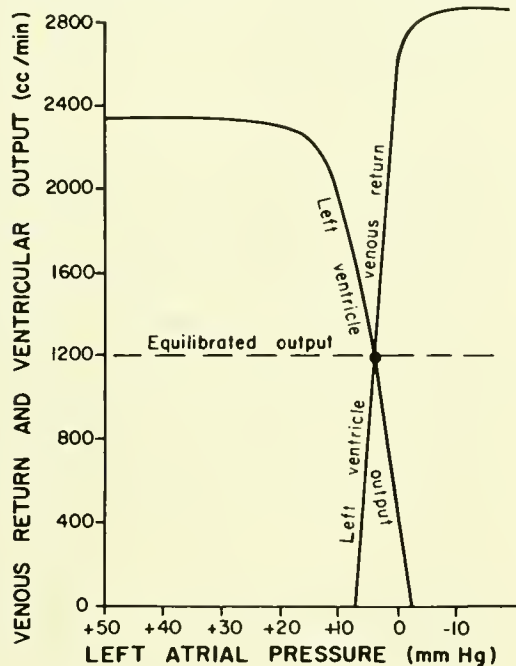


FIG. 22. Transposition of the curves illustrated in fig. 21. This transposition allows the left heart analysis to be correlated with the right heart analysis in the following figures.

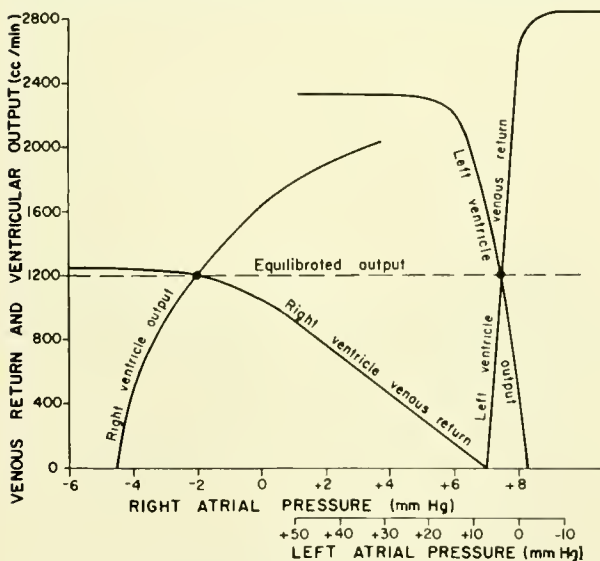


FIG. 23. Simultaneous analysis of left and right heart function, showing that in the steady state the venous returns and outputs of the two sides of the heart are all in equilibrium with each other.

Finally, we superimpose the analysis for the left heart onto a simultaneous analysis for the right heart, as shown in figure 23. In this superimposition, we place the left atrial and right atrial pressure scales so that the 7 mm Hg level of one coincides with the 7 mm Hg level of the other. The reason for this is that our preliminary measurements of mean pulmonary pressure show it to be almost identical in the normal state with the mean systemic pressure, that is, almost exactly 7 mm Hg. Now, we can explain the composite analysis of the two sides of the heart.

Note in figure 23 that the right ventricular output curve and the right ventricular venous return curve equate at the 1200 ml per min level. Likewise, the left ventricular output curve and the left ventricular venous return curve also equate at this same level. Therefore, under normal circumstances the two venous returns and the two ventricular outputs are all equal to each other, and the circulation is in a steady state, without any momentary transference of blood from one of the circulatory segments to another.

BALANCE OF THE TWO VENTRICULAR OUTPUTS WITH EACH OTHER. Proceeding to figure 24, we see the normal situation again depicted by the solid curves. However, the dotted venous return curves represent a situation in which excess blood has momentarily been transferred from the pulmonary circulation to the systemic circulation. Note especially that the two venous return curves intersect the zero venous return

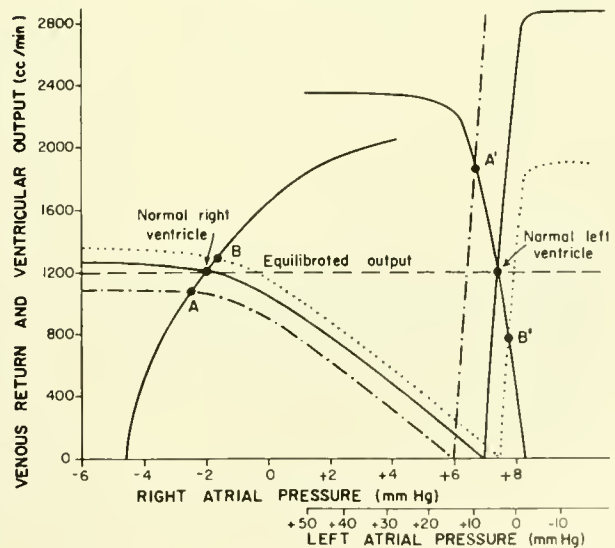


FIG. 24. An analysis showing the manner in which the two sides of the heart automatically balance their outputs. The sequence of events is explained in the text.

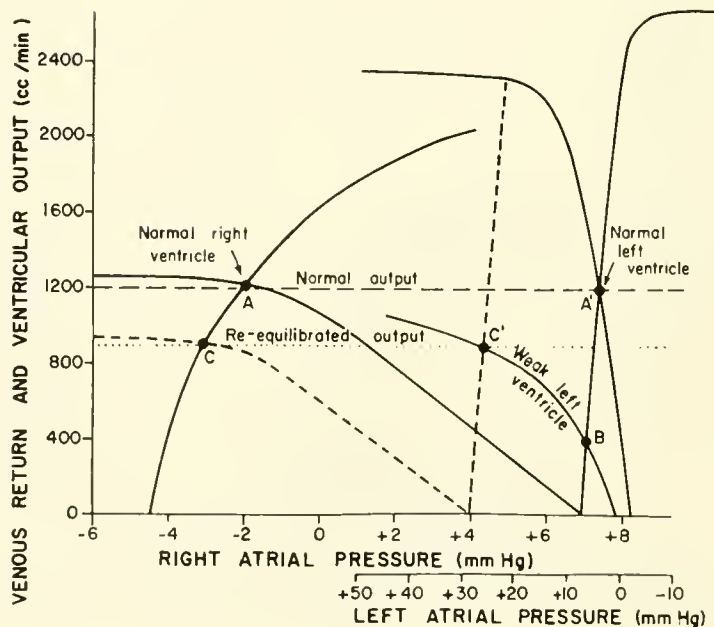
level at the same point, and this point represents the mean systemic pressure on the right atrial pressure scale and the mean pulmonary pressure on the left atrial pressure scale. Thus, the mean systemic pressure has risen from 7 mm Hg to 7.5 mm Hg, and this has caused the right ventricular output to rise to point *B*, a value about 10 per cent above normal. On the other hand, the shift of blood out of the lungs has decreased the mean pulmonary pressure from 7 mm Hg to 3.5 mm Hg, thus shifting the left ventricular venous return curve to the right and decreasing the left ventricular output to point *B'*, an output 40 per cent below normal. This represents a disparity of outputs between the two ventricles of 2 to 1 with far greater amounts of blood being pumped by the right heart than by the left heart. As a consequence, a major shift of blood occurs from the systemic circulation back to the pulmonary circulation, increasing the mean pulmonary pressure and decreasing the mean systemic pressure. As a result, the outputs of the two sides of the heart once again become equilibrated.

Conversely, a sudden shift of blood from the systemic circulation into the pulmonary circulation is illustrated by the dashed-dot curves, showing a decrease in mean systemic pressure to 6 mm Hg and a rise in mean pulmonary pressure to 14 mm Hg. The net result is diminution of right ventricular output by approximately 10 per cent and enhancement of left ventricular output by approximately 40 per cent. Here again there is almost 2 to 1 disparity between

the outputs of the two ventricles, thus resulting in a rapid shift of blood out of the lungs into the systemic circulation; this shift continues until the right ventricular output rises to equal the falling left ventricular output. In this manner, the outputs of the two ventricles once again become re-equilibrated, thus explaining the experimental findings of many different investigators that the two sides of the heart always automatically re-equilibrate with each other within a few heartbeats (11, 18, 129, 159).

EFFECT OF ACUTE LEFT HEART FAILURE ON CARDIAC OUTPUT, VENOUS RETURN, LEFT AND RIGHT ATRIAL PRESSURES, MEAN SYSTEMIC PRESSURE, AND MEAN PULMONARY PRESSURE. Figure 25 illustrates the sequence of events that occurs when the left ventricle suddenly fails. Point *A* is the normal equilibrium point for the right ventricle and point *A'* the normal equilibrium point for the left ventricle. These two are in equilibrium with each other. Then, suddenly, the left ventricular output curve falls to less than one-half normal as depicted by the lower solid curve. Instantaneously, this depressed left ventricular output curve equilibrates with the normal left ventricular venous return curve at point *B* which represents only 30 per cent of normal output. Now a 70 per cent disparity exists between the momentary right ventricular output and the momentary left ventricular output, this causing blood to shift into the lungs from the systemic circulation (138, 139). In a matter of a few heartbeats the new venous return curves become the dashed

FIG. 25. Effect of sudden reduction in pumping effectiveness of the left ventricle. This shows a shift of both venous return curves (as illustrated by the dashed curves) to the left until right ventricular output falls (point *C*) to equal the rising left ventricular output (point *C'*).



curves of the figure, with the systemic venous return curve being governed by a new mean systemic pressure of only 4 mm Hg and the pulmonary venous return curve being governed by a very high pulmonary pressure of +28 mm Hg. Blood continues to shift from the systemic circulation into the pulmonary circulation until the output of the left ventricle rises to equal the falling output of the right ventricle. These conditions are reached at equilibrium point *C* for the right ventricle and equilibrium point *C'* for the left ventricle. Since the mean pulmonary pressure has risen to 28 mm Hg, the pulmonary circulation has become engorged with blood, and the pulmonary capillary pressure will probably be above the critical value of about 25 mm Hg, above which pulmonary edema begins to appear (94).

This is only a partial analysis because within the next 30 sec or so sympathetic reflexes will elevate at least three of the curves, the right ventricular output curve, the systemic venous return curve, and the left ventricular output curve, thereby resulting in a further elevated equilibrium level of cardiac output but also further increase in atrial pressures.

EFFECT OF ACUTE RIGHT HEART FAILURE. Figure 26 illustrates the sequence of events when the right heart fails acutely. Points *A* and *A'* represent normal conditions, and point *B* represents the instantaneous effect of the acute failure on right heart output, showing that the right heart output is only about one-half the output of the left ventricle at that point. Immedi-

ately, blood begins to shift from the pulmonary circulation into the systemic circulation (138, 139), and this shift continues until the left ventricular output falls to equal the rising right ventricular output. The new equilibrium points are *C* for the right heart and *C'* for the left heart, both of which now have the same ventricular outputs and venous returns of 700 ml per min. During the re-equilibration of blood between the systemic and pulmonary circulation, the mean systemic pressure has risen from 7 to 7.4 mm Hg, while the mean pulmonary pressure has fallen from 7.0 to 4 mm Hg. This minute increase in mean systemic pressure explains the failure of systemic vascular pressures to rise greatly in acute right heart failure (122, 181). After another moment or so, sympathetic reflexes tend to elevate the different curves as explained above, and the cardiac output can return part way toward normal.

EFFECT OF BLOOD VOLUME CHANGE. Figure 27 analyzes the effect of hemorrhage on the outputs of both ventricles. Note that the primary effect of reduced blood volume is to shift the scales for left and right atrial pressures, moving the zero pressure points toward each other. An increase in blood volume causes exactly the opposite effect. Here again, since the capacitance of the pulmonary circulation is only one-seventh that of the systemic circulation, the left atrial pressure scale is still one-seventh that of the right atrial pressure scale. Thus, in figure 27, the mean systemic pressure has fallen to 1.7 mm Hg and the

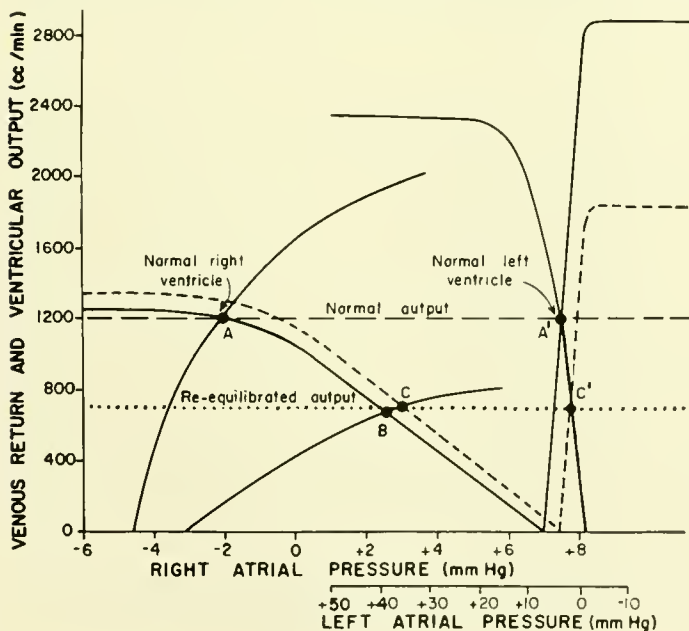


FIG. 26. Analysis of the effect of sudden right ventricular weakness on cardiovascular dynamics showing a decrease in right ventricular output to point *C* and left ventricular output to point *C'*.

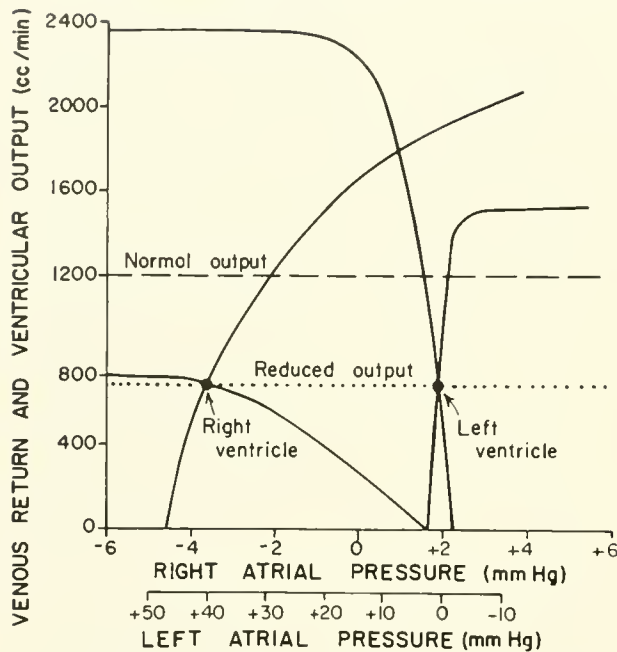


FIG. 27. Effect of reduced blood volume on cardiovascular dynamics. This figure shows that the mean systemic pressure and mean pulmonary pressure are both greatly reduced, thus causing corresponding decreases in the two venous return curves.

mean pulmonary pressure to 2.5 mm Hg. Thus, the net effect of a decrease in blood volume is simply to reduce both the mean systemic and mean pulmonary pressures. This does not affect, at least temporarily, the output curves of either the left or the right ventricles until sympathetic reflexes occur. Also, it does not affect, at least temporarily, the slopes of the two venous return curves. Therefore, the only significant effect is a reduction in both the systemic and pulmonary venous return curves because of the reduced mean systemic and mean pulmonary pressures. As a consequence, both the right ventricular and left ventricular outputs are reduced, in this instance to approximately 55 per cent of normal.

SUMMARY OF THE COMPLEX ANALYSIS. This more complex analysis of the circulation has been presented to illustrate a method for analyzing the effects of unilateral excess load or unilateral alteration in pumping effectiveness of the heart. It has particular importance in analyzing abnormalities of the pulmonary circulation. On the other hand, as one can readily see from the last few figures, even when relatively large quantities of blood shift into or out of the pulmonary circulation, rather small changes occur in the dynamics of the systemic circulation. Therefore,

from a practical point of view, when one is concerned principally with systemic effects of the circulation, the simplified analysis is usually quite adequate.

Obviously, only a few examples of the vast number of uses of these two types of analysis have been given. Because of the multitude of different quantitative values that can be assumed by different venous return and different output curves, the analyses can likewise assume literally thousands of different forms. However, the various alterations in the individual curves that can occur under many different circulatory conditions obey rather simple principles. Therefore, in almost any circulatory condition, one can either establish the different curves experimentally or can predict them very accurately, and from these he can proceed with an analysis of the different effects which will occur in the circulation, particularly as they relate to venous return, cardiac output, left and right atrial pressures, pulmonary blood volume, and systemic blood volume.

SPECIFIC FACTORS THAT AFFECT VENOUS RETURN

Thus far, we have considered only a general analysis of venous return. Now we need to consider several factors that at times play highly significant and specific roles in the local process of blood flow along the veins. These include especially the effects of *a*) the venous pump, *b*) the collapse factor, *c*) central pressure pulsations, and *d*) local factors in the tissues that help to govern venous return such as local tissue activity and tissue utilization of oxygen.

EFFECT OF THE VENOUS PUMP ON VENOUS RETURN. Almost every student of physiology is already familiar with the function of the so-called "venous pump." That is, all peripheral veins beyond the visceral cavities are supplied with valves oriented toward the heart, and any factor that causes successive compressions of the veins exerts a pumping action that propels blood toward the heart. The different types of compression that have been implicated in the venous pump include *a*) compression incident to muscular movement either as a result of direct muscular pressure on the veins or indirectly as a result of movements of the joints and tissues, and *b*) pulsatile compression of the veins caused by arteries lying in the same sheaths as the veins. The second of these has not proved to be of any particular significance. Therefore, the venous pump is also frequently called simply the "muscle pump" (16, 17, 27, 49, 155, 156, 191).

In quiet standing, blood from the legs returns to the heart only with great difficulty, and the pressures in the veins of the lower limb rise to values equal to the weight of blood between the lower limbs and the heart, that is, to as much as 90 mm Hg. However, during walking, the venous return from the lower limbs will be so satisfactory that venous pressures in the feet may be as low as 20 to 25 mm Hg (156). In the absence of an active venous pump, a person can develop such high pressures in the lower part of the body when he stands that he actually loses as much as 15 to 20 per cent of his blood volume in less than one-half hour, thereby in many instances provoking fainting.

EFFECT OF VENOUS COLLAPSE ON VENOUS RETURN. The phenomenon of "venous collapse" is based on the simple fact that it is impossible to suck fluid through a collapsible tube. Since the heart is located in the thoracic cavity where the pressure is normally approximately -5 mm Hg and since the right atrial pressure often is also in the range of -2 to -3 mm Hg, suction frequently is applied to the central veins. This is particularly true of the veins entering from above downward when a person is in an upright position, because, under these conditions, the negative hydrostatic pressure of the blood flowing downward toward the heart adds to the negative pressures al-

ready in the chest, thus causing essentially complete collapse of the veins in the neck. However, this, too, is a very old story known by almost every student of physiology (34, 54-58, 112, 114, 170), and it can be summarized by simply saying that any factor which makes the right atrial pressure more negative than normal does not cause a significant increase in venous return. That is, the venous return will be as great when the right atrial pressure is approximately -2 mm Hg as it will be should the right atrial pressure fall to as low as -15 mm Hg. For instance, when a person breathes air from a chamber that is under negative pressure, this negative pressure is transmitted through his lungs to the chambers of his heart. Yet, breathing against the negative pressure does not increase the venous return to values above normal—all because the veins collapse any time there is an attempt to suck blood from the periphery.

Venous collapse also occurs whenever pressure is applied to the outside of the veins. This very frequently occurs in the case of elevated abdominal pressure (24, 88). Figure 28 illustrates the effect of intra-abdominal pressure on the pressure along the inside of the inferior vena cava. In these studies, a catheter was introduced upward from the femoral vein until it entered the right atrium, showing that the venous pressure all along the extent of the intra-abdominal veins was always slightly greater than

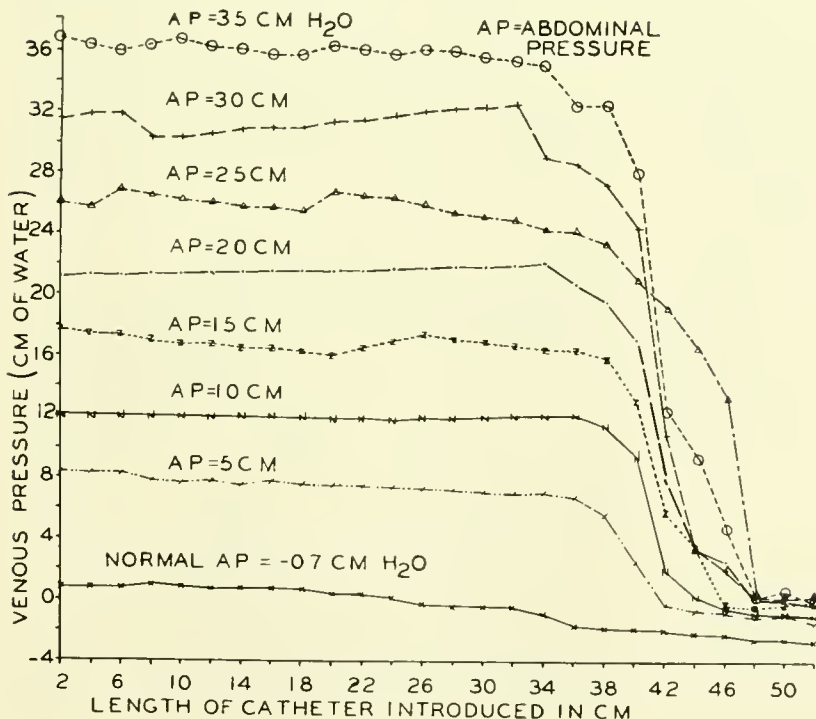


FIG. 28. Effect of increased abdominal pressure (*AP*) on pressures measured from the tip of a catheter inserted up the femoral vein and along the vena cava until it entered the right atrium. [From Guyton & Adkins (88).]

the intra-abdominal pressure. In other words, for blood to flow through a vein as it returns toward the heart, the pressure inside the vein must be greater than the pressure applied to the outside of the vein. If the abdominal pressure is 25 mm Hg, then the pressure in all the lower veins of the body that feed blood through the abdominal cavity, including the leg veins, must be greater than the 25 mm Hg intra-abdominal pressure. Likewise, if a bone or some other structure presses against a vein with a pressure of 10 mm Hg, the pressure in the vein beyond that point must rise above 10 mm Hg to force blood past the compression point. These are simple hydrodynamic principles.

EFFECT OF CENTRAL PULSATION ON VENOUS RETURN.

Probably the most extensively studied factor that has been considered to affect local venous flow is central pulsation. There are two different types of central pulsation which can affect blood flow to the heart. These are 1) increases and decreases in venous pressure resulting from the contractions of the heart itself (6, 21, 30, 124, 185), and 2) increases and decreases in central venous pressure resulting from respiration (1, 28, 32, 33, 62, 130, 149, 187). All studies that have ever been reported on phasic blood flow from the peripheral veins to the heart have demonstrated that the flow of blood toward the heart increases greatly during the negative phases of the central pressure pulses. Then, during the positive phases, blood flow becomes markedly reduced and can even flow backward from the right atrium into the veins. A very significant inflow of blood into the right atrium occurs during inspiration for two different reasons: First, movement of the diaphragm downward decreases the intrathoracic and right atrial pressures slightly, which helps to move blood toward the heart. Second, and much more important, downward depression of the diaphragm compresses the veins of the abdomen, thus forcing large quantities of blood toward the heart. Brecher and his colleagues (31) have recently been foremost among a long line of investigators, extending back a hundred years, in pointing out the phasic flow of blood to the heart caused by central pressure pulsations.

Still more important to our present discussion, however, is not whether or not blood flows into the heart in greater amount during the negative phase than the positive phase but, instead, whether or not central pulsation on the average aids venous return. Different investigators in the past have gone so far as to state that central pulsations are among the most

important of all the factors tending to return blood to the heart, while others have gone so far as to state that, if anything, central pulsations are harmful to the venous return rather than beneficial. Brecher's monograph on venous return presents very admirably the first point of view (31). On the other hand, studies from our own laboratories during the past year have indicated that central pulsations on the average (though not during the negative phases of the pulsations) cause considerable diminution of venous return rather than enhancement (91). For this reason, it would be impossible for the author to present any arguments in favor of the importance of central pulsations in returning blood to the heart. Therefore, the reader is referred to Brecher's thorough monograph for this point of view.

The basis for our belief that central pulsations are harmful rather than helpful, on the average, to venous return is depicted in figure 29. This shows the typical venous return curve, and it shows by means of the horizontal sine waves the central pulsation excursions, varying in this instance between the values -6 and $+2$ mm Hg. The figure then shows by the vertical pulsations the effects of these pressure changes on venous return as would be predicted from the venous return curve. Note that venous return is considerably depressed during the positive phase of the pulsatile cycle. On the other hand, venous return is only slightly increased during the negative phase. Therefore, the average venous return is decreased approximately 10 per cent as a result of the central venous pulsation.

To test this premise experimentally a cannula was inserted in the wall of the right atrium, and varying quantities of blood were injected and removed from the right atrium at frequencies varying between 60

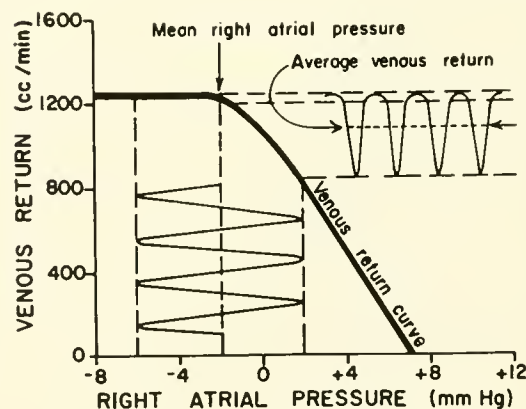


FIG. 29. Effect of central pulsations on venous return, illustrating a rectification phenomenon that causes depressed venous return when central pulsations occur.

and 160 cycles per min and in volume between 0 and 64 ml per cycle. In over 200 successive records not a single instance of increased venous return occurred. On the contrary, even the minutest increase in right atrial pulsation always reduced venous return, and very intensive pulsations actually reduced venous return (at any given mean right atrial pressure) to as low as 50 per cent of normal. Thus, there is a "rectification phenomenon" occurring in the venous return to the heart. That is, on the negative pressure cycle collapse of the veins prevents very much enhancement of venous return, while on the positive pressure cycle, no such event prevents the positive pressure from reducing venous return (29, 36, 37, 44, 113, 118, 141, 151). The net effect, based on both theoretical grounds and experimental grounds, and supported by studies from other laboratories as well as from our own (54), is that central pulsations are not of any value in promoting venous return.

EFFECT OF LOCAL TISSUE ACTIVITY ON VENOUS RETURN—EFFECT OF OXYGEN USAGE BY THE TISSUES. The best known condition in which local tissue activity affects venous return is muscular exercise, in which case the venous return may be increased several fold. Earlier it was pointed out that this is caused both by an increase in mean circulatory pressure and by vascular dilatation in the muscles. The problem still remains, however, to explain the cause of the vascular dilatation in the muscles which in turn leads to the greatly enhanced venous return. In recent years, much evidence has accumulated that oxygen usage by the tissues might well be the initiating factor that controls vascular dilatation (9, 41, 45, 51, 64, 65, 77, 79, 119, 125, 136, 190, 199). Some research workers have felt that relative oxygen lack in the tissues causes them to form a humoral substance which then causes vasodilatation (7, 8, 15, 153). Humoral substances that have been suspected are carbon dioxide, hydrogen ions, adenosine phosphate compounds, histamine, and lactic acid. Thus far, however, none of these substances has been isolated in sufficiently large quantities from the blood to prove that it is truly acting as a vasodilator substance.

Another concept is that the tissue cells compete for the available oxygen in the arterial blood with the vascular smooth muscle, perhaps with the smooth muscle of the metarterioles and precapillary sphincters (45). If the tissues utilize excess oxygen, then the blood vessels will be without adequate oxygen. As a result, these vessels might dilate simply because their smooth muscle walls cannot remain contracted

in the face of oxygen lack. This concept is supported by the following experiment: venous blood was removed from the right ventricle, and arterial blood was removed from the aorta of the same dog at the same time. These two bloods were then alternately passed through an isolated hind limb of a dog in which the input and outflow pressures were controlled and in which the blood temperature was very exactly controlled. The arterial blood always caused vasoconstriction, while the venous blood always caused vasodilatation (to 250% of the arterial value). Furthermore, the degree of vasodilatation depended almost proportionately on the degree of unsaturation of the blood entering the limb as shown in figure 30. The only difference between the two bloods was that one had passed through the lungs and the other had not. Therefore, if any vasodilator substance were in the venous blood, then it would have to have been removed by the lungs. Since the lungs are not known to have this ability to remove vasodilator substances of any type, and since controlled breathing of carbon dioxide illustrated that carbon dioxide had no significant local effect on peripheral vascular flow, we must presume that it is lack of oxygen that initiates the vasodilatation in the limb and not some intermediary vasodilator substance.

The reason for discussing this oxygen lack theory of peripheral vasodilatation so completely is that, in the final analysis, it may be oxygen usage by the tis-

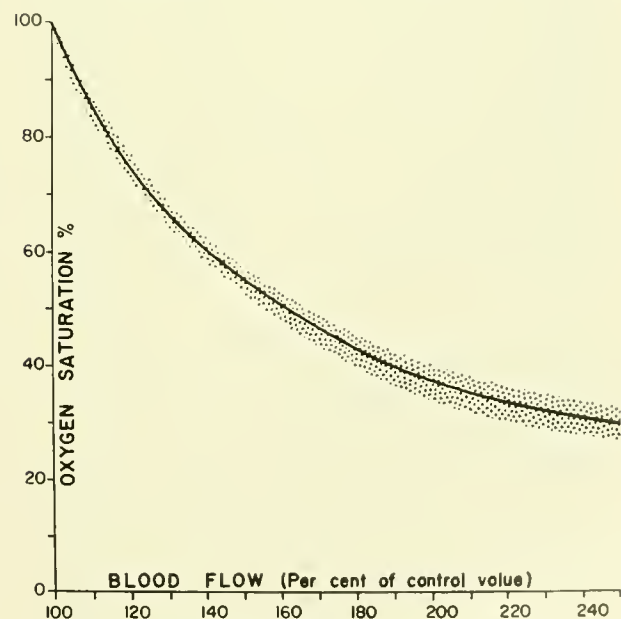


FIG. 30. Effect of reducing arterial oxygen saturation on the blood flow through an isolated hind limb of the dog. [From Crawford *et al.* (45).]

sues that is the primary factor which normally regulates venous return and, therefore, also cardiac output. That is, the degree of local dilatation of peripheral vessels would increase with each increase in local tissue activity; consequently, the return of blood to the heart would be governed by tissue utilization of oxygen. On summing all the individual flows through all the individual tissues of the body we obtain a summated value which equals venous return, and, since this automatically equates with cardiac output, the summated flows of the individual tissues are also equal to the cardiac output. Therefore, if it is true that oxygen lack in all individual tissues does cause vasodilatation, then we find that in the final analysis the rate of local oxygen utilization could be the single most important controller of venous return and cardiac output. Indeed, this is supported by many isolated studies of the relationship between oxygen utilization or oxygen lack and circulatory blood flow, beginning with the study of Douglas & Haldane (51) in 1922 in which it was shown that oxygen lack increases the cardiac output to a considerable extent, and extending through studies by Gorlin and co-workers showing a greatly increased cardiac output in severe oxygen lack (77), and a more recent study by Huckabee (119) showing an increase in cardiac output of as much as twofold in animals poisoned with cyanide.

Besides the acute peripheral dilatation that results from oxygen lack, a very marked additional increase in tissue blood flow occurs over a period of several weeks if excessive oxygen usage or oxygen deficiency persists for this long period of time (130a). This, however, results from increased "vascularity" of the tissues, that is, increased numbers of blood vessels. Nevertheless, this too, despite its slowness to develop, represents a very important and very powerful regulatory mechanism for control of venous return in response to oxygen need by the tissues.

Aside from the experimental observations on the control of venous return and cardiac output by oxygen lack, there is one compelling theoretical reason for believing that oxygen lack should be the main controller of venous return and cardiac output, and that is the following: Of all the essential substances supplied to the tissues by the blood, oxygen is by far the one most critically dependent upon an adequate blood flow. For instance, blood flow can be decreased to as little as $1/20$ normal, and adequate quantities of glucose, fats, and proteins can still be carried to the tissues. Also, if the depth of breathing

is increased, carbon dioxide can be carried away from the tissues in adequate quantities even when the cardiac output is decreased to as little as $1/10$ normal. On the contrary, the tissues become severely damaged from anoxia whenever cardiac output remains only slightly below normal for a prolonged period of time. Therefore, it is readily obvious that oxygen transport to the tissues is normally markedly "flow limited," while the transport of no single other essential substance to or from the tissues is limited to a significant extent under normal or anywhere near normal conditions. For this reason, it is especially reasonable that oxygen should be the major regulator of venous return and cardiac output; this would provide a closed loop regulatory system that would help to maintain an adequate supply of oxygen to all the tissues at all times.

VENOUS PRESSURES

The regulation of venous pressure is inextricably related to the regulation of venous return and cardiac output, as has already been pointed out in both the simplified and more complex circuit analyses presented earlier in this chapter. All the different significant factors which affect right atrial pressure have already been discussed. On the other hand, the right atrial pressure is not the same as the more peripheral venous pressures. Therefore, we need now to conclude our discussion of the return of blood to the heart by summarizing the different factors that determine the peripheral venous pressures. These include, first and paramount, the right atrial pressure itself. In addition, they include *a*) resistance to blood flow along the veins, *b*) rate of blood flow in the veins, and *c*) hydrostatic pressure effects.

EFFECT OF RESISTANCE TO FLOW IN THE VEINS. Dilated central veins are so large that they have almost no resistance to blood flow, but semicollapsed veins, on the other hand, have very high resistance. This effect is particularly important at the different compression points where the veins pass over the ribs or lie against some relatively solid organ (52, 53). In the ordinary circulation, therefore, the resistance to venous flow is not negligible, principally because of the compression points against the veins. On the other hand, when the right atrial pressure rises to a very high value, blood can dam up in the veins, elevating the pressures in the veins to values equal

to or perhaps considerably greater than those on the outside of the veins. In these instances the vein become distended and the venous resistance becomes automatically reduced. This turns out to be an important safety factor in venous return, for often an elevated right atrial pressure results from a damaged heart, in which case return of blood to the heart would become inadequate if the venous resistance should remain as high under these conditions as it is in the normal circulation. Fortunately, however, the reduced resistance of the veins allows the existing pressure gradient from the periphery to the heart to force blood toward the heart almost equally as well as it occurs normally. For this reason, the peripheral pressures ordinarily do not rise significantly until the right atrial pressure has risen above approximately +4 to +6 mm Hg (74). Above this point, the veins by then will have become distended, and any additional rise in right atrial pressure is there- after reflected by a similar increase in peripheral venous pressure (83).

EFFECT OF VENOUS FLOW ON PERIPHERAL VENOUS PRESSURES. An increase in the volume of venous blood flowing toward the heart theoretically would cause essentially the same effects on peripheral venous pressures as would an increase in venous resistance. However, from a practical point of view this is not true, because an increase in volume of flow normally simply distends the collapsed veins to a greater degree, thus reducing the resistance to flow. The flow and decreased resistance ordinarily compensate for each other so that increasing the flow has relatively minor effect in increasing the peripheral venous pressures rather than a major effect as might be expected (88). This has been demonstrated especially in the case of blood flowing from the peripheral limbs through the abdominal cavity when the intra-abdominal pressure is elevated. For instance, if the intra-abdominal pressure is +10 mm Hg, whether the flow from the leg to the right heart is 0.5 ml per min or 200 ml per min, the pressure in the femoral vein leading into the abdominal cavity still remains only 1 mm Hg or so greater than the 10 mm Hg intra-abdominal pressure.

EFFECT OF HYDROSTATIC PRESSURE ON PERIPHERAL VENOUS PRESSURES. Finally, we have the well-known effect of hydrostatic forces on peripheral venous pressures. That is, the simple weight of the blood increases the venous pressures in the dependent

parts of the body and creates negative pressure in areas above the heart. The collapse factor and the venous pump that modify these pressures were described earlier in the chapter. Particularly important is the fact that the veins of the neck collapse and their resistances automatically become greatly elevated. Therefore, venous pressure in the neck almost never falls below atmospheric pressure unless unusual circumstances prevent the veins from collapsing.

Because of the importance of the hydrostatic factor in all venous pressure measurements, two very similar methods have been suggested for determining a "physiological zero" pressure in the venous system (93, 111). The second of these, which was presented from our laboratory, depends on rotating a dog about two different axes. It was found that venous pressures referred to a point barely inside the right ventricle at the tricuspid valve did not vary a measurable amount regardless of the position of the animal.

SUMMARY

To summarize this entire chapter, its important point has been that one cannot analyze venous return separately from a simultaneous analysis of many other factors in the circulation. However, relatively simplified analyses, based principally on four major segments of the circulation, the right heart, the pulmonary circulation, the left heart, and the systemic circulation, can provide an almost complete understanding of the interrelationships between *a*) venous return, *b*) cardiac output, *c*) right atrial pressure, *d*) left atrial pressure, *e*) mean systemic pressure, *f*) mean pulmonary pressure, *g*) mean pulmonary volume, and *h*) mean systemic blood volume.

If we should choose any single factor that might be the primary regulator of venous return, and hence also the primary regulator of cardiac output, it might be the tissue utilization of oxygen. Certainly, in over half of the tissues of the body if not in the entire body, local blood flow seems to be controlled by the local utilization of oxygen, and the summated value of all the local flows is the venous return. Therefore, oxygen utilization by the tissues might well be, in the final analysis, the primary regulator of venous return.

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Effects of ions on vascular smooth muscle¹

SYDNEY M. FRIEDMAN

CONSTANCE L. FRIEDMAN

*Department of Anatomy, The University of
British Columbia, Vancouver, Canada*

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INTRODUCTION

General Physical Chemistry of Ions

We are here concerned only with pointing out in simplified form the basic physical-chemical features of ions and the manner in which these affect their role in biological processes. For detailed treatment of this subject the reader is referred to standard chemistry texts as well as to the basic articles of Conway (31, 32), Hodgkin (112) and Shanes (182, 183).

OSMOTIC EQUILIBRIUM. We may begin by considering osmotic pressure to be the equivalent of the mechanical pressure which must be applied to a solution to prevent osmosis of the surrounding solvent into the solution through the membrane. It is, therefore, not

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primarily a characteristic of the membrane but is a measure of some real difference between pure solvent and solution. The membrane merely allows this difference to show itself.

The osmotic pressure, Π , of any solution is proportional to temperature and concentration:

$$\Pi = kCT$$

Accordingly, in dealing with a cell, we must consider the osmotic pressure not only of the solution inside the cell but also that of the environment which bathes it. The cell contains an amount of nondiffusible material in solution which is essential to its metabolism. Clearly, the amount of this material which can be retained without causing the cell to swell will be sharply limited unless there is also a counterbalancing nondiffusible material outside its membrane. This is perhaps the major niche into

which evolution has fitted the sodium ion. Cell membranes are almost impermeable to this ion and, since the cellular nondiffusible material is almost constant, the amount of cellular water is controlled by variations in extracellular sodium, Na_o . Conway (31) has demonstrated this point by showing, for example, that K concentration in the medium, K_o , can be varied over wide limits without influencing the basic dependence of cell volume on Na_o after equilibration (fig. 1). This essential point is often overlooked in experiments dealing with alterations of the medium.

The development of osmotic pressure is one of the colligative properties of solutions. Ideally it is determined by the number of particles in solution:

$$\Pi V = nRT$$

Its expression, however, depends on whether or not the membrane is permeable to the particle in question. At equilibrium, no osmotic pressure is exerted by a particle to which a membrane is freely permeable.

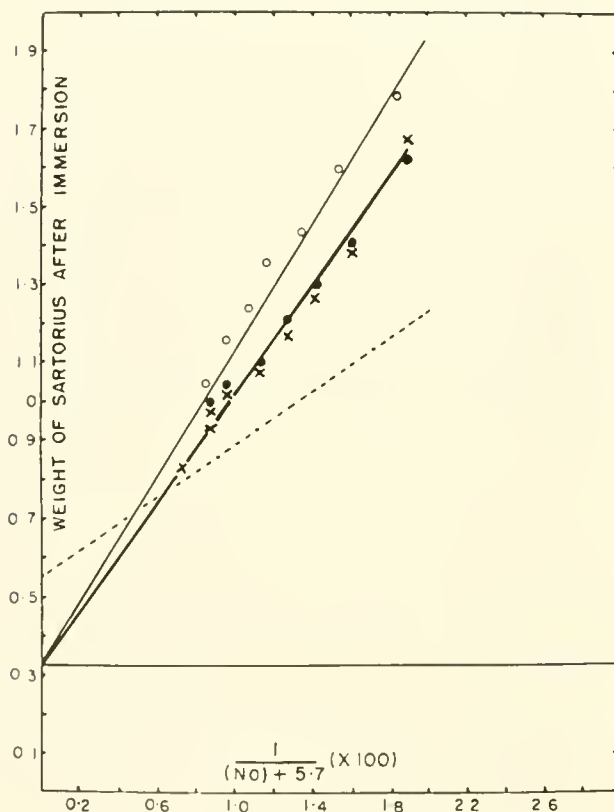


FIG. 1. The dependence of sartorius weight on $[\text{Na}^+]$ of the medium (24-hour immersion at 3 C). Closed circles: stepwise NaCl reduction replaced by KCl. Crosses: stepwise NaCl reduction not replaced by KCl. Open circles: stepwise NaCl reduction in the presence of cyanide (2×10^{-3} M). Volume control at equilibrium depends on $[\text{Na}^+]$ even in the presence of cyanide and is independent of $[\text{K}^+]$ above maintenance level (20 meq/liter). [From Conway (31).]

ION SIZE. Ions may be defined as particles which have gained or lost an electron on passing into solution. The elements of Group 1 of the periodic table, the alkali metals Li, Na, K, Rb, and Cs, are all characterized by possessing a single electron in their outer orbital shell. In solution this is lost so that the element loses its electroneutrality and remains positively charged as Li^+ , Na^+ , etc. Other elements, like those in Group 7, take up one or more electrons into their outer shell and so become, in solution, negatively weighted, e.g., Cl^- , Br^- , I^- , etc. The formation of ions is not restricted to elements but also occurs with more complex radicals which can collectively gain or lose one or more electrons, e.g., OH^- , NH_4^+ , etc.

Ions share the ordinary colligative properties of substances in solution as, for example, freezing point depression, osmotic pressure, etc. Additionally, they possess a number of special properties based on the fact that they are electrically charged.

We must distinguish here the size of the ion considered as a solid ball, so to speak, and defined by its crystal radius, from its size when associated with water molecules and defined by its hydrated radius. The increase in size of the monoatomic crystals of Group 1 falls naturally into the same order as their periodic arrangement $\text{Li} < \text{Na} < \text{K} < \text{Rb} < \text{Cs}$.

For many years it has been the accepted practice to emphasize the hydrated ion in biological systems.

TABLE 1. *Ionic Radii of Alkali Metal Ions*

| | Crystal Radius, Å | Hydrated Radii, Å From Mobility |
|------------------------------|-------------------|------------------------------------|
| Li | 0.60 | 2.31 |
| Na | 0.95 | 1.78 |
| K | 1.33 | 1.22 |
| Rb | 1.48 | 1.18 |
| Cs | 1.69 | 1.16 |
| NH ₄ ⁺ | 1.48 | 1.21 |

From Ussing *et al.* (202).

The smaller the ionic crystal the more densely is its electrical field packed and the greater its attraction for water dipoles. Consequently, the size of the package, crystal plus water, moving in a solution, is larger the smaller the crystal. Thus, the rank order for the hydrated ion size is Cs < Rb < K < Na < Li (table 1). This model should not be accepted uncritically (160) although it does provide us with a useful working framework.

ION ACTIVITY. Ions in solution are subject to interionic forces which limit their availability. In consequence, the measured concentration of an ion may be greater or less than its reactive concentration by some measurable degree defined as the activity coefficient. The concentration of the substance, corrected by the activity coefficient, defines the activity of the ion in the given solution. Since reactions in solutions and their resultant equilibria are determined by activities rather than by concentrations this point has special importance. As figure 2 shows, each salt has its own characteristic curve relating activity to concentration. Standard tables are available. For similar reasons, the ionization constant of salts is also of import, since not all salts dissociate with equal completeness into ions. Activity will be symbolically written (Na⁺) and concentration [Na⁺]. Where such precision is not necessary in a given context we shall simply write Na for sodium or Na⁺ for sodium ion.

ION MOBILITY. In general, the mobility of an ion in free solution varies inversely with its hydrated size. In fact, the concept of ion hydration was in part developed to explain the relative mobilities of ions. Ion mobility is ordinarily measured as velocity in a standard electrical field. Table 2 shows the relation of increasing size to slower velocity.

ION PENETRABILITY OR MEMBRANE PERMEABILITY. Cell membranes in general appear to have channels so limited in size as to allow K to enter freely and just

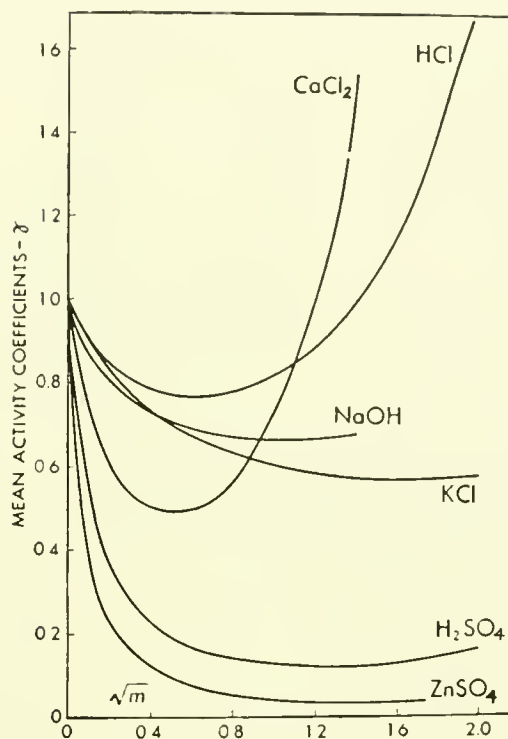


FIG. 2. Mean activity coefficients of various electrolytes at 25 C. [From Prutton & Maron (161a).]

to exclude Na. Conway (32) has presented interesting and basic data pertinent to this point (table 3). Frog sartorius immersed in Ringer fluid, to which 100 mm of a particular salt is added, at first loses weight (osmotic withdrawal of water). Then, if the membrane is freely permeable to the salt, the weight increases back to its original base. Thus, at equilibrium, the added salt has not upset the osmotic balance. The time required to recover 50 per cent of the weight loss is taken as a measure of the permeability of the membrane for the particular ion and table 3 is so constructed. It is evident that taking KCl as standard, RbCl and CsCl enter readily, while the chlorides of Na, Li, Ca, and Mg do not enter appreciably. Similarly, in the anion series, bromide and nitrate enter easily while phosphate, acetate, bicarbonate, and sulfate are excluded.

On the right side of the table Conway compares the diffusion coefficients of the ions rather than relative ion diameter with K and points out that the correspondence is far from exact (cf Rb and Cs penetration rates with diffusion rates).

The permeability of the cell membrane to ions is not a fixed characteristic but must be expected to vary physiologically and pathologically.

TABLE 2. *Relation of Ion Size to Mobility in an Electric Field*

Velocities of Ions Under Gradient of 1 V/cm or 0.5 V/cm for Divalent Ions

| Cations | | Anions | |
|-----------------|-------|---------------------|-------|
| H | 315.2 | OH | 173.8 |
| Rb | 67.5 | Br | 67.3 |
| Cs | 64.2 | I | 66.2 |
| NH ₄ | 64.3 | Cl | 65.2 |
| K | 64.2 | NO ₃ | 61.6 |
| Na | 43.2 | CH ₃ COO | 35.0 |
| Li | 33.0 | SO ₄ | 34.0 |
| Ca | 25.5 | HPO ₄ | 28.0 |
| Mg | 22.5 | | |

From Conway (32).

TABLE 3. *Relative Entrance Rates of Ions into Muscle (Left Column) Compared with Their Diffusion Constants, D, Through Water Relative to K Taken as 100 (Right Column).*

| Cation series | | D for single ions, with K value = 100 | |
|--------------------------------|-----|---------------------------------------|-----|
| KCl | 100 | K | 100 |
| RbCl | 38 | Rb | 103 |
| CsCl | 8 | Cs | 104 |
| NaCl | 0 | Na | 67 |
| LiCl | 0 | Li | 52 |
| CaCl ₂ | 0 | Ca | 40 |
| MgCl ₂ | 0 | Mg | 35 |
| Anion series | | | |
| KCl | 100 | Cl | 100 |
| KBr | 63 | Br | 105 |
| KNO ₃ | 17 | NO ₃ | 96 |
| K phosphate | 4 | H ₂ PO ₄ | 50 |
| KOOC·CH ₃ | 3 | HPO ₄ | 39 |
| KHCO ₃ | 1 | CH ₃ COO | 54 |
| K ₂ SO ₄ | 0 | HCO ₃ | 67 |
| | | SO ₄ | 53 |

From Conway (31).

Special Properties of Ions in Biological Systems

DONNAN EQUILIBRIUM. By thermodynamic principles it can be demonstrated that the product of diffusible cations and anions on the two sides of a membrane must attain equality at equilibrium. Thus:

$$(\text{cations})_i(\text{anions})_i = (\text{cations})_o(\text{anions})_o$$

When the cell is nonpermeable to some charged material on one side of its membrane, a sufficient number of diffusible ions of opposite charge is required to balance this. In the cell this fixed material is mainly negative in charge so that it can be shown that at equilibrium the sum of the diffusible cellular cations must be rather larger than the sum of diffusible anions. In brief, this shows up in the low

Relative Ion Diameters (Diameter of Potassium Ion = 1.00)

| Cations | | Anions | |
|-----------------|------|---------------------|------|
| H | 0.20 | OH | 0.37 |
| Rb | 0.96 | Br | 0.96 |
| Cs | 1.00 | I | 0.97 |
| NH ₄ | 1.00 | Cl | 0.98 |
| K | 1.00 | NO ₃ | 1.04 |
| Na | 1.49 | CH ₃ COO | 1.84 |
| Li | 1.95 | SO ₄ | 1.89 |
| Ca | 2.51 | HPO ₄ | 2.29 |
| Mg | 2.84 | | |

intracellular and high extracellular Cl⁻. It is important to realize that in determining an expected Donnan equilibrium in a tissue only the diffusible ions count. Thus, Na⁺ figures only to the small extent that it penetrates the cell membrane.

ELECTROCHEMICAL GRADIENTS AND MEMBRANE POTENTIALS. It is beyond the scope of this article to attempt to deal with this fascinating subject in any sort of detail. Since our discussion of ions and smooth muscle must make frequent reference to bioelectric potentials, however, a brief outline will be presented.

Two different dilutions of a substance A' and A'' have necessarily different activities and different chemical potentials stored in them. This may be expressed as the change in free energy required to move one mole of A' from the lower to the higher activity or, conversely, the amount of free energy liberated when A'' slides from higher to lower activity. This relation follows the very general form

$$\Delta G = RT \ln \frac{(A)'}{(A)''}$$

ΔG can be expressed in electrical terms as volt-coulombs and factored into a potential difference E and nF faradays so that:

$$E = \frac{RT}{nF} \ln \frac{(A)'}{(A)''}$$

At 25 C this simplifies to

$$E_{(mv)} = 58 \log \frac{(A)'}{(A)''}$$

Clearly, the osmotic balancing of the nondiffusible material in the cell and the associated Donnan rearrangement together produce a situation in which the diffusible ions are distributed unequally on the two sides of the membrane and so contain stored energy.

By far the major diffusible ion concerned is K^+ and so we may write as a first approximation:

$$E_m = \frac{RT}{F} \ln \frac{(K^+)_i}{(K^+)_o}$$

where E_m is the potential at equilibrium across the membrane and i , inside, o , outside. Concentrations are usually written but activities, as shown, are more precise.

The movements of Na^+ and Cl^- are essentially quite limited; yet, to the extent that they are permeable, their distribution must also contribute to the over-all transmembrane potential. Goldman (92) has therefore proposed a constant field equation:

$$E_m = \frac{RT}{F} \ln \frac{(K^+)_i + p(Na^+)_i + p(Cl^-)_o}{(K^+)_o + p(Na^+)_o + p(Cl^-)_i}$$

By convention E_m is regarded as positive. The symbol, p , expresses the permeability of the ion relative to K^+ taken as unity, influx and efflux being considered separately. This equation may or may not be entirely correct but it is applicable to our purpose, since it takes into account the contributions of ions other than K^+ and their relative mobilities.

Special Properties of the Physiologically Important Ions

The particular role of Na^+ and K^+ has already been described. They are the major bulk ions of the body and, in fact, the maintenance of their distribution may consume a major share of the body's energy. Their role has been the subject of comprehensive monographs (61, 202).

Calcium and magnesium, belonging to Group 2 of the periodic table, have in their outer orbital shell two electrons which are given up readily in solution. They may, and probably do, participate in the phenomena described above, but they are also particularly important in enzymatic processes. They are far more readily complexed than either sodium or potassium.

Hydrogen and hydroxyl ions are distinguished by their mobility and easy penetrability into and out of cells. Their primary involvement in acid-base equilibria needs no comment at this point.

The physiologically important anions have also been the subject of an extensive monograph (54).

CLASSIFICATION AND CRITICAL APPRAISAL OF METHODS

It is not our purpose here to describe all the methods used to study the effects of ions on vascular smooth muscle directly or indirectly. The aim is rather to seek the general principles underlying each approach and to indicate to what extent the methods used can further our understanding. On this basis we can classify the methods broadly into two groups: those in which the experimental variable is the cell environment and those in which the vascular tension is the manipulated variable.

Studies of Vascular Smooth Muscle Tension Associated with Manipulation of the Milieu

In these studies the ionic milieu or environment of the cells has been manipulated *in vivo* by varying the dietary salt intake or by loading with various salts given by stomach tube, by infusion, or by injection. In this group we have, too, studies of the effects of hormones known to affect salt metabolism and *in vitro* studies in which the medium has been directly manipulated. Obviously, the more prolonged the treatment and the more general its effects, the more difficult it is to pin down any direct relation between treatment and vascular smooth muscle tension. Even so, all approaches must be examined if we are not to lose sight of important clues.

The effects of these manipulations, of varying degrees of remoteness from the target, have been assessed by three principal methods.

MEASUREMENT OF DIASTOLIC BLOOD PRESSURE. Since a major determinant of the diastolic blood pressure is the peripheral vascular resistance this approach has some limited value. The results can always be attacked on the grounds that a change may indicate an effect on cardiac output, on blood viscosity, or on blood volume, etc., rather than on peripheral resistance. Such studies have value, however, if they correlate well with other more direct approaches. Experiments of this type in the rat suffer still more seriously from the fact that most of the indirect methods do not measure diastolic blood pressure at all but some mixed level which approximates the mean pressure.

MEASUREMENT OF PERIPHERAL RESISTANCE IN REGIONAL VASCULAR BEDS. This approach is necessarily confined to studies of the effects of fairly rapid changes in the milieu. Within this limitation, it can be highly

accurate. The variable of cardiac output can be eliminated by controlling the rate of inflow into the vascular bed with a constant output pump (101). It can remain as a variable when blood flow rate and pressure are monitored simultaneously in the vascular bed under study (148). Additionally, this type of approach can give direct information concerning vascular tonus in different segments of a given bed. At the present time, in vivo studies carried out in this manner are the best available.

The alterations of the environment attainable with this approach are exceedingly limited if the circulation of the bed is continuous with that of the general systemic pool. The imposed change must not be great enough to elicit a systemic reaction and the change of milieu induced must be analytically confirmed. To avoid these difficulties many studies have been carried out using totally isolated vascular beds, e.g., rabbit ear, dog hind limb, rat hind limb, perfused with artificial solutions. The gain in control of the medium does not, however, compensate for the loss of a physiological preparation; hence such studies have not been extensively used for our particular problem.

Microscopic observations of various circulatory beds have yielded useful information concerning the physiology and pharmacology of these beds (114). Because the mesoappendix or meso-omentum, the beds usually studied (217), have rather special properties, they have not been extensively or profitably used to study the effects of ions.

MEASUREMENT OF TENSION IN THE VASCULAR STRIP OR RING OR IN AN ANALOGOUS SMOOTH MUSCLE STRIP. The in vitro approach has the value of enabling the experimenter to control the environment although, of course, the results must later be fitted to the in vivo framework. This type of study has suffered greatly from the fact that, so far, no one has been able to mount a representative of the vessels that actually control peripheral resistance. As substitutes, rings of large arteries or strips of aorta (87) have been used, although Bohr & Goulet (14) have recently reported briefly that a spiral strip of rabbit mesoappendix arteriole may be practicable.

The aorta seems to us a particularly poor choice because of its specialized elastic tissue content. It behaves quite differently from peripheral vasculature in vivo and, in particular, shows a slow and prolonged response time (11, 48, 88). An additional criticism is that the smooth muscle cells are abnormally oriented in the spiral strip. One would hope that a suitable preparation using a length of artery under intra-

luminal pressure distributed radially from its fluid content will soon be devised to replace the present strip techniques. Paton (157) and Davey (44) have both had some success with this approach and our own preliminary studies seem promising. For the present, we must discuss the results derived from current techniques with necessary reservation.

Although it is clear that different types of smooth muscle differ in their drug responses, they do have certain histological features in common. We shall, therefore, round out this part of the discussion by surveying the findings with uterus and gut strips in order to recognize generalizations where possible.

Studies of the Milieu During Manipulation of Vascular or Analogous Smooth Muscle Tension

In these studies, vascular smooth muscle tension has been increased or decreased, acutely or chronically, by a diversity of procedures ranging from hormones through drugs to direct ionic manipulation. Some well-defined parameter outside and/or inside the cell has been measured. The principal analyses are as follows:

MEASUREMENT OF EXTRACELLULAR AND OR INTRACELLULAR IONS AND WATER. The external environment of the smooth muscle cell has for a long time been estimated from measurements chiefly of plasma Na, K, Cl, and Ca. The analytical procedures have gradually been improved but Na determination by flame photometry with greater than 1 per cent error, exclusive of the sampling error, has made the world of small changes in plasma or serum Na unapproachable.

More recently it has become apparent that a knowledge of the extracellular fluid volume is required if extracellular ionic quantities are to have any meaning. The volume distribution of exogenously administered inulin so far gives the most reliable estimate of this (89, 206, 207). Earlier studies used chloride which, under basal conditions, was thought to be almost entirely extracellular. It is now generally realized, however, that not only is the chloride space larger than the extracellular space but also that procedures which alter cation distribution of necessity produce variable chloride shifts for the preservation of electroneutrality within the cell. Accordingly, we must interpret the ion partitions based on chloride measurements with caution. Other substances such as bromide or thiosulfate used as measures of extracellular space suffer from similar criticisms.

TABLE 4. *Some Representative Vascular Tissue Analyses*

| Author | Tissue | Total Na, meq/kg Dry Wt. | Total K, meq/kg Dry Wt. | Total Cl, meq/kg Dry Wt. | Total H ₂ O, ml/kg Wet Wt. | Cell Na, meq/l. | Cell K, meq/l. | Cell H ₂ O, ml/kg Wet Wt. | Inulin Space, ml/kg Wet Wt. | Cl Space, ml/kg Wet Wt. | Na Space, ml/kg Wet Wt. |
|---------------------------|------------------------------|--------------------------------|-------------------------------|--------------------------------------|------------------------------------------------|--------------------|-------------------|-----------------------------------------------|--------------------------------------|----------------------------|----------------------------------|
| Daniel & Dawkins (40) | Rat stomach | 271±14 | 350±8 | | 770±4 | | | | | | |
| Barr (9) | Cat small int. | 322 | 405 | 350 | 810±2 | 65±5 | 108±6 | | 101±17 | 544 | 43 ² |
| Laszt (133) | Rat bladder | 310±0.8 | 352±0.7 | | 784±3 | | | | | | |
| Daniel & Daniel (39) | Immature rabbit uterus | 451±24 | 266±30 | | 792±12 | 101 29 | 100 236 | 522 219 | 270±30 | 573±36 | 613 |
| | Immature cat uterus | 632±43 | 274±3 | | 819±15 | 143 119 | 120 213 | 414 261 | 405±20 | 558±15 | 75 ¹ |
| Tobian & Binion (195) | Human renal art. | 395±71 | 187±36 | | 760±23 | | | | | | |
| Tobian & Binion (196) | Rat aorta | 358±5 | 95±1 | 254±9 | | | | | | | |
| Daniel <i>et al.</i> (41) | Rat aorta | 336±20 | 141±7 | 189 | 646±11 | | | | | | |
| Daniel & Dawkins (40) | Rat aorta | 296±29 | 131±7 | | 664±9 | | | | | | |
| Tobian & Redleaf (200) | Rat aorta | 292±4 | 119±2 | 222±2 | | | | | | | |
| Laszt (133) | Rat aorta | 265±0.8 | 149±0.5 | | 638±6 | | | | | | |
| Dodd & Daniel (49) | Rabbit aorta | 327±44 | 59±16 | | 663±14 | 158 | 192 | | | 483 | 650±48 |
| Sréter (unpub.) | Rat aorta | 227±4 | 109±1.4 | | 659±5 | 92±5 | 113±4 | 322±10 | 337±11 | "corrected" | |

Sample analyses of nonvascular smooth muscle are presented for illustration. Estimate of variance is omitted wherever original data were recalculated to fit the tabular description. Derived data depend on either inulin or chloride space value shown on same horizontal line. (Table prepared by Dr. F. A. Sréter.)

Tissue analyses have also been carried out in an attempt to measure Na, K, and water and their extracellular/intracellular partition under a variety of conditions. Few of these have encompassed a representative vascular tissue, and even these few have been quite incomplete. Table 4 presents basic data taken from the work of several laboratories.

Total aorta Na and K vary from about 200 to 350 and 95 to 150 meq per kg dry tissue, respectively, the variation probably reflecting the animal's age, previous diet, and the sampling method. An aorta sodium so much higher than potassium is consistent with a large extracellular space.

It is apparent that the chloride space sometimes exceeds the readily measured total water content of the tissues and hence is a poor measure of extracellular space. Tobian & Binion (196), for example, reported an extracellular fluid volume based on chloride which recalculates to some 750 ml per kg wet tissue and this exceeds most investigators' estimates of total water. Dodd & Daniel (49) reported a chloride space of 633 and a sodium space of 650 ml per kg rabbit aorta, and again the total tissue water was only 640 to 660 ml

per kg. They argued that there was probably a fraction of bound chloride wrongly included in the calculation. Even after a correction for this, however, they still obtained an extracellular fluid volume of 483 ml per kg.

Using inulin in a revised procedure we estimate extracellular space as about 50 per cent of the total tissue water. This compares favorably with the estimate of Prosser *et al.* (161) of 39 per cent of the total tissue volume.

The ratio of extracellular to total water runs lower in other types of smooth muscle than in aorta. Inulin space measures 12 per cent of the total water in cat small intestine (9) and 34 per cent in the rabbit uterus (39). These again are in line with the electron microscopic observations. [The high inulin space reported for the immature cat uterus (39) is out of line.]

Intracellular Na runs higher in the aorta and in other types of smooth muscle than in skeletal muscle.

MEASUREMENT OF OSMOTIC PRESSURE AND PH. The development of techniques suitable for measurement of osmotic pressure and pH in small samples has made

it quite feasible to study these parameters directly. Unfortunately, these have not been much applied to the problem of ions and vascular tissue. This is an important deficiency.

ELECTRICAL MEASUREMENTS. It is now generally believed that electrical potentials developed across cell membranes depend on ionic distribution, mobility, and the permeability characteristics of the membrane itself. Unfortunately, because of technical difficulties, vascular tissue has not been approached until very recently and only minimal information is available. We shall thus have to lean heavily on electrical measurements obtained from other types of smooth muscle, especially guinea pig taenia coli.

CONTINUOUS MONITORING OF Na OR K ION ACTIVITY. The development of ion-specific glasses responding especially to Na^+ or K^+ (55) has made it possible to prepare electrodes suitable for monitoring Na^+ or K^+ in flowing blood (79). These electrodes can discriminate ion activity with far greater resolution than any methods hitherto available and can also be applied to the analysis of single samples or to the continuous monitoring of activity in a tissue bath. Their application to the problem in hand has only just begun, but already they have furnished several important pieces of information.

ROLE OF SODIUM AND POTASSIUM IN VASCULAR SMOOTH MUSCLE TENSION

Evidence from Studies of Diastolic Blood Pressure or Reactivity

GENERAL RELATION OF Na AND K TO CLINICAL AND EXPERIMENTAL HYPERTENSION. More than 50 years ago Ambard & Beaujard (4) suggested that the development of clinical hypertension was abetted by salt, although they incorrectly stressed Cl^- rather than Na^+ . Allen & Sherrill (2) revived the idea some 25 years later, correctly identified Na^+ as the important ion, and urged the use of low salt diets in treatment. After a period of neglect the idea recurred when Kempner (126) advocated the unpalatable rice diet for hypertensive patients and indeed, in so doing, came close to starting a food cult (27). Shortly thereafter the main therapeutic benefit of the rice diet was distinguished from its psychological benefit and shown to reside in its low sodium content (34, 98, 159). By the beginning of the last decade the low sodium diet

was firmly established as a measure of limited but certain usefulness in the management of the hypertensive patient. Because of difficulties inherent in its use it could not be widely applied but, even so, patients were routinely encouraged to reduce their voluntary salt intake for fear of accelerating the progress of their disease.

The effort to reduce the amount of sodium available to the body in hypertension led naturally to attempts to increase its loss through the kidneys. This approach was dramatically successful as specific natriuretic agents, such as chlorothiazide and hydrochlorothiazide, were developed and shown to be highly effective in the treatment of hypertension (1, 8, 97). These agents show clearly that as long as the kidneys are competent, the simple desalting of the body will reduce an elevated diastolic blood pressure and, even though normotensive levels may not be attained, will tend to keep it down.

Studies of experimental forms of hypertension have also underlined the general relation between available salt and blood pressure. This was first shown by the fact that hypertension induced by the prolonged administration of desoxycorticosterone acetate (DCA) is accelerated by concomitantly increasing the salt intake (179). This effect was shown to be specifically due to the sodium ion (180). A slower blood pressure rise can be induced without adding extra salt to the intake above that supplied by the food, but no rise occurs if the diet is sodium-free (18, 84, 181). A similar dependence on Na intake has been found to obtain for the hypertension which occurs during adrenal regeneration (184, 185) and in the subtotaly nephrectomized animal (128). Thus far, most forms of experimental hypertension respond to Na deprivation or depletion with a reduction in blood pressure (194).

The implication of Na metabolism in the hypertensive process has also been sharply underlined by studies of the response of man and animals to acutely imposed salt loads. The results have been strikingly uniform and the accelerated excretion of such loads, first systematically demonstrated in various forms of hypertension in the rat (77, 93), is also a consistent feature in hypertensive man (35, 94).

There is reliable but not so extensive evidence implicating K in a general way with the hypertensive process. Most of these studies have come from M. Friedman and his associates. These investigators first pointed out that the rise in blood pressure produced by renal compression in the rat can be reduced by prolonged K deprivation (6 weeks) and argued that this effect is related to the decrease in smooth muscle

tonus known to occur in gut and urinary bladder during potassium deficiency (72, 170, 210). An adequate K intake was also shown to be essential for the development of DCA hypertension although, unlike the effect of Na, an excessively high K intake does not accelerate the process (68, 169). In later studies, these authors concluded that the effect of varying the K intake depends on its simultaneous relation to the Na intake and that the development of hypertension depends on a high K/Na ratio (167, 169). This important theme will recur in our later discussion. Perera (158) confirmed the basic observation by showing that essential hypertension in man could be reduced by a low K diet, although this was not a practicable therapy.

EFFECTS OF VARYING NA AND K INTAKE OR LOSS ON BLOOD PRESSURE. Sapirstein and associates first reported in 1950 (172) that rats given various hypertonic NaCl solutions to drink develop an arterial hypertension after a latency of 1 to 4 weeks. This was confirmed by Toussaint *et al.* (201) and extended by Meneely and his collaborators (151, 152) who showed that the rise in blood pressure in such salt fed animals is proportional to their salt intake. A latter report from this same laboratory (150) pointed out that the effect of adding NaCl to the diet can be partly offset by a simultaneous increase in K as well. From this, they suggested that the blood pressure rise is dependent on an increase in the Na/K ratio. This is diametrically opposite to the work of M. Friedman and co-workers, cited above, which implicated a high K/Na ratio.

Fregly (71) has sharply underlined the importance of salt as a determinant of vascular resistance. He has recently produced hypertension in the adrenalectomized salt-fed rat and has shown the relation of the blood pressure rise to the amount of salt ingested. Vick *et al.* (203) found that vascular sensitivity, measured as the response of the aorta strip to epinephrine, increased in rats after 10 to 15 weeks of high salt feeding.

The idea that an excessive intake of salt may itself be a sufficient etiological factor in essential hypertension has been staunchly supported. In an extensive series of studies Dahl and his colleagues (36-38) have attempted to relate the incidence of hypertension in man to his salt-eating habits. Others have studied areas of reputedly high or low salt intake in order to relate the incidence of hypertension to the dietary habits of the inhabitants (176, 194). So far, however, the evidence that Na intake plays a primary etiological role is still shaky.

A serious deficiency in Na may occur naturally during exposure to excessive heat; the advance of the deficiency is associated with vascular collapse (100). Excessive salt depletion for therapeutic purposes may produce a similar picture (175). In the rat, acute Na depletion may be readily induced by equilibrating an intraperitoneal isosmotic mannitol or sucrose solution with the extracellular compartment. Such a depletion is always accompanied by hypotension (unpublished observation).

Although the prolonged intake of large amounts of K does not affect the blood pressure of the normotensive rat, K restriction is an effective hypotensive procedure (66). The depressor effect depends on the associated Na intake, for it does not occur in the presence of a low, but only with a normal to high intake (67). Such K-deficient hypotensive rats show a marked decrease in pressor response to epinephrine, norepinephrine, angiotensin, and renin (168). Both basal blood pressure and reactivity are rapidly restored by KCl given subcutaneously (72).

These highlights selected from an extensive literature show the limitations of this type of approach. They also show, however, that sodium and potassium can be implicated in the regulation of blood pressure and that sodium in particular plays some kind of critical role in hypertension. Unfortunately, too many steps intervene in the processes to permit any kind of valid interpretation. Even as far as this type of information is concerned we are faced with a major omission, for there is no assessment of the possible role of water in relation to salt intake. Sapirstein (171), in an attempt to reconcile the conflicting evidence, has drawn attention to the importance of water in the renal handling of electrolytes. It is evident that animals given various salt solutions to drink are confronted in each case with a fixed ratio of salt to water, and an ensuing rise in blood pressure may reflect either the increased salt ingestion or the inability of the animal to make an adjustment in its water intake. Similarly, in states involving salt loss, any speculation must also take into account the simultaneous changes in water distribution. McCance & Morrison (143) have pointed out this unsatisfactory aspect of experiments which do not distinguish between salt and water as separate variables.

Evidence from Studies of Tension or Reactivity of Vascular or Analogous Tissue

EFFECTS OF MANIPULATION OF NA IN THE MEDIUM. There is consistent evidence that the exposure of

smooth muscle to a sudden reduction of Na concentration in the medium, Na_o , osmotic pressure being held constant, produces an immediate increase in tension (116). This increase in tension is not sustained as equilibration proceeds. Streeten & Vaughan Williams (189) noted an increase in motility of intestinal loops (dog) during the first stage of Na depletion by intraperitoneal lavage. Whitehead (208) noted an increase in tone of isolated ileal or jejunal segments (rabbit). We (78) studied the response in greater detail using a colon strip (rat) suspended in a sensitive strain-gauge tensometer and found that the increase in tension and the duration of response are proportional to the degree of reduction of Na_o . Dodd & Daniel (49) observed a similar immediate increase in the tension of an aorta strip following a reduction in Na_o .

The sudden reduction of Na^+ in the medium must at once unbalance ionic equilibrium across the smooth muscle cell membrane. The restoration of equilibrium, while still retaining electroneutrality in each compartment, may require a migration of positive ions from within the cell to the exterior. Since K ions are the only ones freely available for this they must shift outward (31, 32). The increase in tension recorded may be primarily related to the applied reduction of the Na gradient, Na_o/Na_i , or perhaps to an induced K^+ efflux from the cell.

We may suppose that, with time, the Na gradient is gradually built back up toward its basal state as Na is actively but relatively slowly extruded. Thus, when fully equilibrated, tissues in a low Na medium contain a reduced intracellular Na concentration, Na_i . Working with guinea pig taenia coli, Holman (118) has shown that at this stage the tissue still responds normally to stimuli, but Bohr *et al.* (13) claim hyperresponsiveness for the vascular strip. Daniel's group does not agree with this (49). When such tissues are equilibrated in very low levels of Na_o , however, all agree that they become first hyposensitive and finally unresponsive (49, 116, 118, 147, 188, 189). This suggests that the response falls off either because Na_i reaches some critical level or that Na_o/Na_i has itself fallen below some critical value.

The observation that tone or responsiveness or both decline after equilibration in very low Na_o seems quite uniform. The experiments of Dodd & Daniel (49) and Yamabayashi & Hamilton (214) show that the phenomenon applies equally well to vascular smooth muscle. It appears, however, that a fairly extreme reduction in Na_o is necessary to elicit this change and, since techniques vary, there is no uniform

answer concerning the absolute level at which the hyporeactivity occurs. Indeed this level may also vary in different types of smooth muscle (43). We shall later see whether the decline in responsiveness after equilibration in low Na media can be related to a reduction in the Na_o/Na_i gradient.

The time used by various workers for equilibration of their tissues varies over a wide range. This may well condition the responses obtained, since all tissues incubated in vitro for any length of time (in hours) take up Na and water and may extrude some K (165). Put another way, these tissues fail to maintain a normal sodium gradient. This process is accelerated by cooling and is more marked in artificial than in natural media, for example, plasma.

Despite the detailed differences between the experimental results with various smooth muscle types, we may conclude that, in general, an induced reduction in the sodium gradient produces an immediate increase in tension, while the continued presence of such a low gradient leaves the tissue less primed for the next stimulus, that is, hyporesponsive. Several additional observations now fall into line and a few of these may be dealt with at this point. Hughes *et al.* (120) found that rat uterus immersed in normal Krebs solution for 3 hours gained Na_i , as do all tissues, and became less responsive to test doses of histamine. We have incubated dog femoral artery in Krebs solution at 0°C overnight, a situation in which the cells must gain Na (165), and in the morning find the tissue contracted and totally incapable of responding to drug stimulation. Rewarming to 37°C, the standard procedure for re-extruding Na, relaxes the tissue and restores its responsiveness. McDowall & Zayat (145) have concluded that smooth muscle (uterus) takes up sodium during drug-induced contraction and in this state is less responsive to stimulation.

McDowall & Soliman (144) suggest that the post-stimulatory refractoriness is due to difficulty in repriming the cell by extruding Na. In brief, they relate unresponsiveness to the simple increase in Na_i and support this idea by the fact that responsiveness can be quickly restored to a refractory uterus strip by reducing Na in the medium. Three facts militate against this oversimplified explanation. In the first place, the acute reduction of Na in the medium can be expected to facilitate Na extrusion but only during the prolonged equilibration period. In fact, however, the reduction of Na_o restores responsiveness at once. In the second place, as we have pointed out earlier, the sudden reduction of Na_o immediately unbalances

the cell's ionic relation with its environment and may demand an efflux of K ions; this may be the basic process. This is supported by the fact that under similar circumstances, responsiveness can be as well restored by increasing K in the medium. In the third place, as described above, hyporesponsiveness occurs also in extremely low Na media when Na_i must necessarily be very low rather than high as after stimulation. Clearly, however, a reduction in the Na gradient is common to both hyporesponsive situations.

If an increase of tension in smooth muscle is ordinarily associated with a shift of Na from outside to within the cell as McDowall & Zayat (145) have suggested for uterine muscle and as we shall later suggest is a general process, we can distinguish in this the importance of the Na gradient. Thus, we (78) have shown that contraction of a colon strip, induced by a variety of agents, can be aborted by adding Na to the medium. This procedure affects only Na_o and not Na_i and thus directly implicates the Na gradient in the induction of the tension increase and not the simple intracellular gain in Na considered alone. We shall later associate these changes with K distribution as well.

There is reasonably consistent evidence concerning the events following exposure of a smooth muscle strip to a medium containing supranormal Na concentration. If the concentration of Na is high enough, the first response appears to be an increase of tension which is sustained for some minutes (10 or so) and then declines to subnormal levels as equilibration proceeds. This has been shown to apply to guinea pig taenia coli (116) and to the dog aorta strip (214). The increase in tension can be partially but not entirely attributed to an increase in osmotic pressure of the bathing solution. Other authors who did not raise Na_o quite so extremely noted no change in tension, but agree that tissues so exposed become hyporesponsive to drug stimulation. We (78) recorded such a decline in reactivity of the colon strip following exposure to even moderate elevations of Na_o. Williamson & Moore (209) observed that a rise in Na_o and a fall in K_o, either individually or in combination, caused a lessened response of the isolated rabbit aorta strip to norepinephrine. Similar findings were reported earlier by Bohr *et al.* (13). We cannot account for the observation of an increase in responsiveness to epinephrine under similar circumstances (214).

Although the complexity of the procedures and responses used to study this problem almost defy rational interpretation, several fundamental facts do emerge.

1) Vascular smooth muscle, like other types of smooth muscle, responds to sudden reduction of Na_o with a temporary increase of tension proportionate to the degree of change in the medium. Tension declines as equilibration proceeds.

2) After equilibration in moderately low Na_o media, the responsiveness of vascular smooth muscle is unchanged or increased. At critically low levels of Na_o the tissue becomes hyporesponsive.

3) Vascular smooth muscle exposed to high Na_o may show a temporary increase in tension, but very high levels of Na are required for this.

4) After equilibration in high Na_o media the responsiveness of vascular smooth muscle is substantially reduced.

5) Studies of the effects of ions must distinguish between immediate effects which reflect a temporary instability and later effects which depend on the new equilibrium.

EFFECTS OF MANIPULATION OF K IN THE MEDIUM. Although the procedures and responses vary a good deal, it has been found that most types of smooth muscle increase their tension upon exposure to a potassium-enriched environment. The older literature has been reviewed by Evans (60) and the more recent by Goffart & Bacq (91). The latter authors indeed go so far as to point out that the potassium-induced contraction can be used as a basic procedure for the study of agents which enhance (sensibilize) or inhibit the response. The following reports are typical of the studies carried out and of the results obtained.

Holman (118) studying guinea pig taenia coli reported that at first a reduction of K in the medium produced little effect. After a few minutes, however, tension began to fall and on prolonged exposure low levels were reached and maintained.

Exposure of the uterus of the rat, guinea pig, rabbit, or cat to an elevation of K in the medium produces an immediate contraction (190). So, too, the intestine strip shows an immediate increase in tension (3, 118, 147, 204). Cantoni & Eastman (28) observed that the temporary depression which follows maximal contraction of the guinea pig intestine exposed to histamine, acetylcholine, pilocarpine, barium chloride, or Mecholyl can be overcome by a small increase of K in the medium. Similarly, Hazard & Cornec (107) found that small amounts of K increased the response of the rat duodenum to acetylcholine.

In general, vascular tissue follows similar patterns. As early as 1926 Gellhorn (90) attempted to place a series of cations in a rank order based on their effects

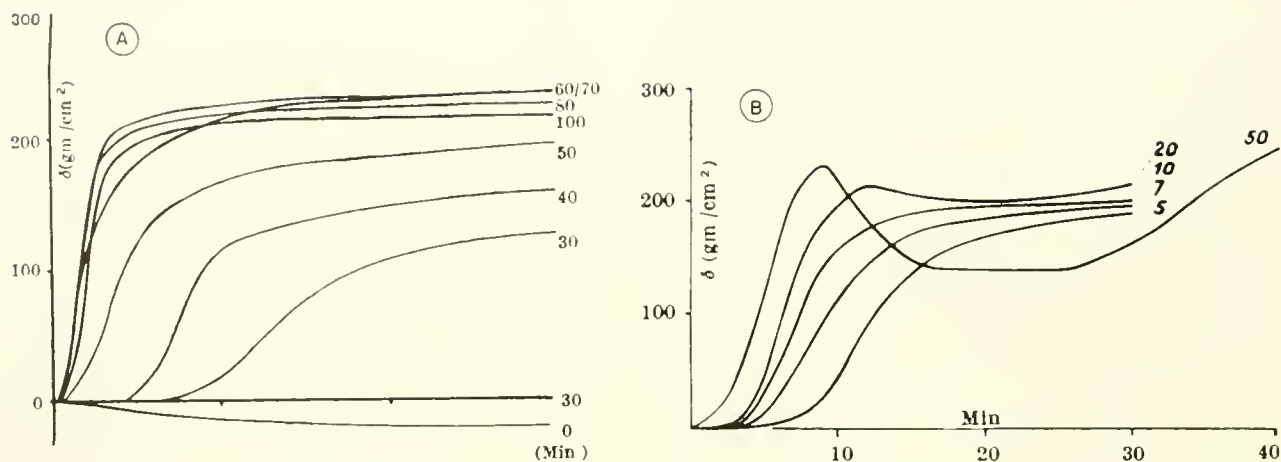


FIG. 3. Tension changes in carotid artery strips on exposure to different concentrations of A, K^+ and B, Cs^+ . Concentration of the cation in millimolars appears at the right of each line. [From Laszt (135).]

on an isolated aorta strip. He pointed out that the addition of Li^+ relaxed the strip and that Na^+ produced no obvious change, while NH_4^+ , Cs^+ , Rb^+ , and K^+ in that ascending order caused increasing degrees of contraction. He did, however, use fairly extreme quantities, adding in each case 3 ml of an isotonic concentration of the chloride to 10 ml of Tyrode's solution. In effect he raised the K concentration of the medium to about 50 meq per liter.

Furchgott & Bhadrakom (88), in the course of pioneer studies which established the rabbit aorta strip as a standard test object, observed the effects of more moderate increases in K_o . They noted that contraction followed if the K level was raised to three- or fourfold normal. The addition of smaller amounts of K, sufficient only to double that of the normal medium (Krebs), did not cause visible contraction but did potentiate the response to low doses of epinephrine.

Bohr *et al.* (13) confirmed and extended these findings. Using the Furchgott procedure, they noted a marked increase in the response of the aorta strip to norepinephrine when the medium K was doubled. Additionally, they observed a marked and progressive reduction of responsiveness in a K-free medium. More recently, Barr *et al.* (10) studied the responsiveness of dog carotid artery strips stored in the cold and then rewarmed. Stored in the cold, 4°C, these strips, like most tissues (165), gained Na_i and lost K_i , and with this their responsiveness declined. The recovery of maximal responsiveness was roughly parallel to the steady-state K reaccumulation during the progression of rewarming. Williamson & Moore (209) observed that the sensitivity of the rabbit aorta strip varied

with changes of K in the medium in a manner inverse to Na. Thus, lowering Na or raising K, singly or in combination, increased the sensitivity to norepinephrine. Conversely, raising Na or lowering K, singly or in combination, decreased the norepinephrine-induced contraction. Dodd & Daniel (49) also pointed out that contractile responses increase in a high K medium. They observed a transient increase of sensitivity in a K-free medium as well, but this rapidly yielded to the usual reduction in responsiveness observed by most workers.

Laszt (133-135) has recently produced unequivocal evidence relating tension and the concentration of K in the medium (fig. 3). Using a carotid artery strip (specified only as from "cattle") this worker has shown that the stepwise elevation of K_o produces a stepwise increase in tension. The threshold concentration of cesium (5 mM) or rubidium (10 mM), which can similarly induce a contraction when added to the medium, is less than that required for potassium (30 mM), and this Laszt considers to be direct evidence relating the effect to ion size. Similarly, the tension induced by equal concentrations of cesium, rubidium, and potassium chloride shows the same dependence on rank order. The interpretation which this investigator places upon these findings argues that the tension increase is a function of the rate at which Cs^+ , Rb^+ , or K^+ can move into cells. This neglects the fact that the ability of ions to cross cell membranes is not an exclusive function of their hydrated radius (see table 3).

One group of observations stands alone and contrasts sharply with the examples cited above. In these a reduction of K_o is reported to be associated with

hyperexcitability (140), while an increase in K_o reversibly abolishes the ability to contract (47). These two rather baffling reports, although stemming from different authors, are united in one major respect: the artery preparation was driven electrically rather than by means of a known physiologically active mediator.

Although once again we find that it is difficult to equate the complex procedures used and the complex results obtained, several fundamental facts emerge.

1) Vascular smooth muscle, like other types of smooth muscle, responds to the sudden reduction of K_o with little immediate change.

2) As equilibration in low K_o media proceeds, the responsiveness of vascular smooth muscle and its basal tension progressively decline to reach a new low level which is steadily maintained for long periods. The experiment of continuing to lower K_o by successive washout has apparently not been attempted.

3) Vascular smooth muscle exposed to high K_o (at least fourfold normal) shows an increase in tension proportionate to the increase in K_o , and this is usually sustained. Responsiveness too is increased in high K_o media.

4) Time is an important variable in the responses studied—too often an insufficiently considered variable.

5) In general, there is a suggestive inverse relation between K_o and Na_o .

Evidence from Studies of Resistance in Regional Vascular Beds

EFFECTS OF NA INFUSIONS. It is exceedingly difficult to attempt to alter only one constituent of a perfusing solution in an *in vivo* preparation and still remain within the bounds of physiological decency. Even so, considerable progress has been made in demonstrating that at least some of the *in vitro* observations have important implications for vascular homeostasis. We shall now examine the major lines of these investigations, noting especially where they are consistent with the evidence already cited.

All workers who have infused Na salts into the arterial circulation have observed peripheral vasodilatation. Eliakim *et al.* (56) observed a fall in systemic blood pressure in the dog on injecting 1 ml per kg of 20 per cent NaCl fairly rapidly. We (78) observed that Na salts depress diastolic and systolic blood pressure in the rat even in the presence of a simultaneously administered pressor agent. Katz & Lindner (125) perfused the coronary arterial circulation in the dog with defibrinated blood in a classic

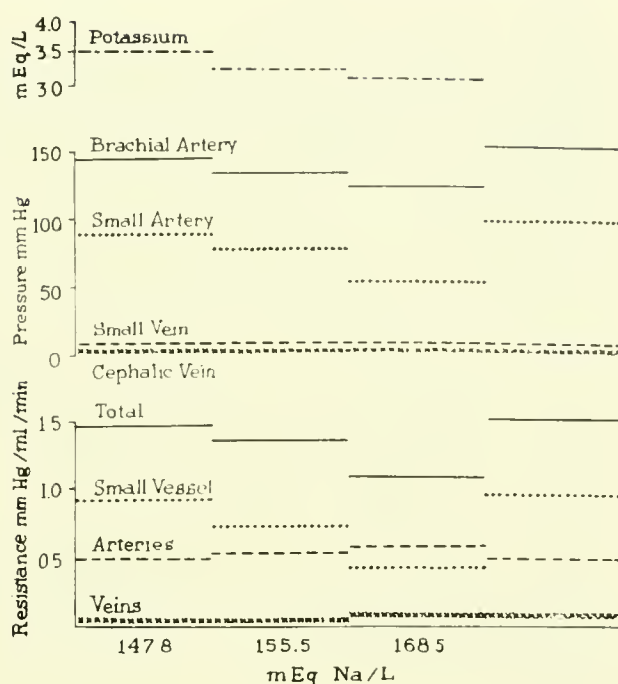


FIG. 4. Relation of serum $[Na^+]$ in venous outflow to vascular pressures and resistances in the dog forelimb. Average of 11 animals. Ten per cent NaCl infused into brachial artery at 0.6, 1.0, 2.3, and 0.0 ml/min in that order. [From Haddy (101).]

series of experiments and observed that even fairly small additions of Na produced vasodilatation.

Marshall & Shepherd (148), in a beautiful series, used the newly developed ultrasonic flowmeter to monitor flow in the femoral artery of the dog and studied changes in limb resistance in response to Na salts. They found that the rapid injection of 2 ml of 10 to 20 per cent NaCl produced vasodilatation. The same effect was obtained with a continuous infusion of the same solutions at 2.3 ml per min. A series of other salts (citrate, lactate, bicarbonate, acid and alkaline phosphate) all produced the same effect. Binet & Burstein (12) obtained similar results in the dog limb isolated from the circulation of the rest of the body, except as perfused under control from the systemic circulation through a constant pressure pump.

Haddy and his associates have used perhaps the most detailed and elegant technique to study this same problem. Basically, these workers perfuse the forelimb of the dog with arterial blood rerouted from the femoral artery. The connecting polyethylene tubing uniting the femoral to the brachial artery passes through a constant output pump which operates by intermittent compression of the tubing. Pressure

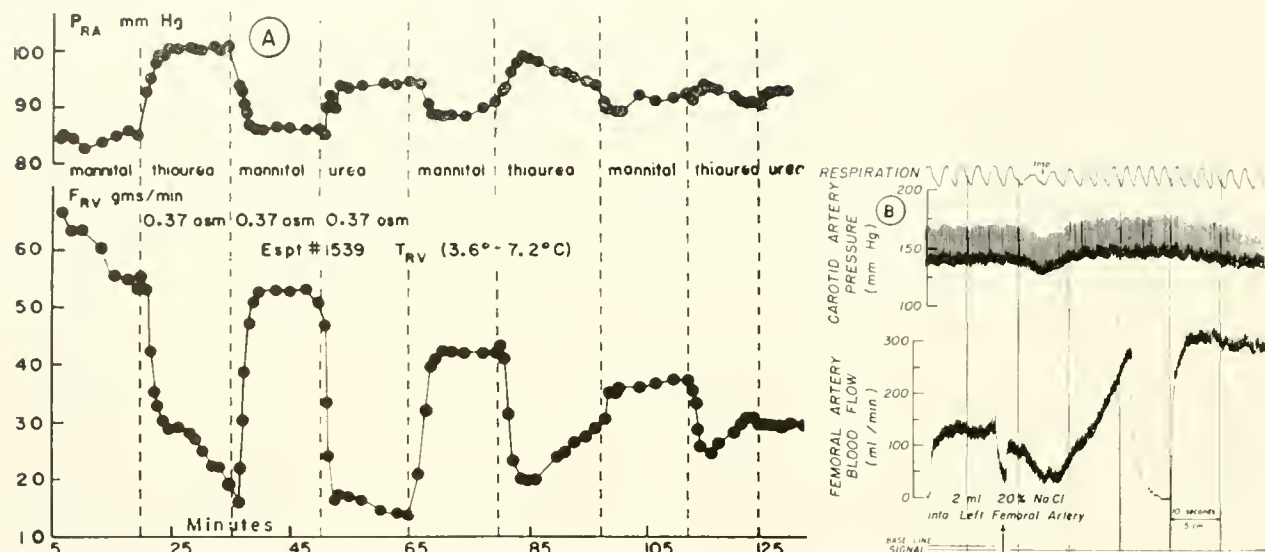


FIG. 5. *A*: changes in renal vein flow, F_{RV} , and renal artery pressure, P_{RA} , with perfusate composition changes. T_{RV} = temperature of renal vein outflow. [From Harvey (104).] *B*: effect of hypertonic saline solution on blood flow through femoral artery measured with ultrasonic flowmeter. Note the zero calibration check at the beginning of the record and again during the period of increase in flow. The fall in flow rate at time of injection is an artifact. [From Marshall & Shepherd (148).]

is monitored by means of fine cannulae passed into the vascular tree at several points distal to the pump so that a detailed description of the resistance of the various segments of the circulation can be compiled. Haddy (101), too, found that amounts of NaCl, insufficient to alter systemic pressure, produced arteriolar dilatation in the dog forelimb.

Unfortunately, it is not possible to elevate plasma Na concentration in the perfusing blood without at the same time raising its tonicity. Marshall & Shepherd (148) first noted this as an experimental defect and found that they could obtain a similar degree of vasodilatation by infusing dextrose and urea matched for tonicity to their sodium salts and concluded that the mechanism of vascular relaxation was uncertain. Muirhead *et al.* (154) had earlier noted this effect of hypertonic infusions. This point led Overbeck & Haddy (156) to restudy the problem. They found that hypertonic solutions of NaCl, Na_2SO_4 and Na_2HPO_4 , which produced the same final serum Na concentration, evoked decreases in limb vascular resistance in parallel with their actual tonicity. Equally hypertonic infusions of Na_2SO_4 , and NaCl, irrespective of the amount of Na supplied, evoked equal decreases in small vessel resistance. They concluded that the addition of Na apparently had little or no independent effect apart from that of its tonicity. On the other hand, these same workers (102) have obtained some evidence that a reduction

of Na in the perfusing medium is slightly vasoconstrictive and decreases the caliber of the small vessels. Harvey (104) and Read *et al.* (164) have studied the effects of hypertonic solutions on the renal vascular bed and have arrived at the same conclusion regarding the relation of hypertonicity of the infusion and its vasodilatory effect.

These findings are in substantial agreement with those obtained with vascular and other smooth muscle strips studied *in vitro*. It will be recalled that following exposure to high Na_o such tissues may show a temporary increase in tension, but very high levels are required for this. On the other hand, after equilibration in such high Na media, tension is usually lower than normal and responsiveness of these tissues is reduced, and this obtains *in vivo* as well. Thus, following perfusion of the rat with Na salts we (86) found the blood pressure responses to norepinephrine and to Pitressin sharply reduced. Haddy (101), in more precise studies, has shown this to be due to a reduction in the responsiveness of peripheral vessels to both pressor and depressor agents. Since this effect persists, it may not be directly related to the osmotic effect of the hypertonic solution.

It should be emphasized that an osmotic effect produced by infusing a hypertonic solution cannot, in fact, be dissociated from an ionic effect. The withdrawal of water from cells causes a proportionate

increase in both Na_i and K_i . We shall deal with the quantitative aspects of this type of shift later.

EFFECTS OF K INFUSIONS. Attempts to link the effects observed in vitro to in vivo responses of vascular tissue have necessarily been limited in scope. This again reflects the technical problems limiting such exploration.

Mathison (149) long ago produced what is still one of the best pieces of work on this subject. He injected a few milliliters of $M/7$ (isotonic) KCl into the arterial circulation of the cat. A rise in blood pressure followed at once; this was also obtained in the decerebrate, spinal, or spinal-pithed animal. The effect was not of cardiac origin and was only partly due to excitation of vasomotor centers, since a considerable rise of pressure was still obtained after ergotoxine. This author paid careful attention to tonicity, anion control, and pH. He pointed out also that peripheral vascular relaxation rather than constriction followed the injection of less concentrated solutions beginning at $M/11$. Hoff *et al.* (115) obtained much the same result.

Hazard & Quinquaud (108) carried out an exceedingly nice pharmacological study of the pressor effect of intra-arterially injected KCl. They showed that a large part of the effect was due to adrenal medullary discharge. Then, using a series of blocking agents, they came to the conclusion that a significant part of the vasoconstrictive action of K was directly exerted on vascular smooth muscle.

McKeever and associates (146) perfused the left coronary in the dog with blood from a donor animal, interposing a constant output pump in the line (cf 101). KCl was then added at constant rate to raise plasma K from 2 to 20 meq per liter. Except at the very lowest concentrations the infusions produced a transient dilatation of large and small arterial segments lasting for about 1 min, followed by a more sustained constriction. Still higher concentrations were entirely constrictive, but the degree to which an adrenal discharge may have contributed was not assessed.

Emanuel *et al.* (58) have carried out a careful analysis of the changing pattern of resistance in the different segments of the dog forelimb during infusion of K salts and have correlated their findings with systemic and local measurements of serum Na and K. Small vessel resistance decreased at all infusion rates. By contrast, arterial resistance did not change at lower rates and then, as the rate increased, gradually began to show an increase. The net effect of these

changes was an over-all fall in resistance at low rates and a rise at higher ones. The primary phenomenon held for increases in serum K up to about 8 meq per liter, at which point the secondary net constrictive effect appeared. The arterial constrictive phase may be in large part related to adrenal discharge. These results were similar for the chloride, nitrate, lactate, and acetate. They applied equally well to the renal vascular bed (178). Even these moderate elevations of K_o reduced the sensitivity of the peripheral vasculature to challenging doses of pressor and depressor agents.

The work of this group satisfactorily explains the phase of falling peripheral vascular resistance noted by all authors who have infused small amounts of KCl. It also shows that K does not produce smooth muscle vasoconstriction in the physiological range and agrees in this with in vitro studies. It leaves unexplored, and correctly so, the effect of high, unphysiological amounts of K which are vasoconstrictive in vitro. This latter point has great theoretical importance if a change in membrane potential is involved in peripheral vasoconstriction. Unfortunately, the experimenter cannot explore the problem in vivo, for although high K infusions do not, like Na, raise problems of osmotic pressure they do produce adrenal, cardiac, and nervous effects which presently defy rational interpretation.

Speaking critically, the perfusion of regional vascular beds is not a totally satisfactory approach to the problem. Technically, many of the procedures give detailed information concerning the responses of each segment of the vascular bed and for this are most satisfactory. The problem resides not in this facet of the approach but in the attempt to alter a single variable in the medium while still perfusing with whole blood. Such a situation cannot be fully controlled. Using the Na and K electrodes we have found many times that the solution we thought was presented to the cells was not the same as the solution the cells actually met. To interpret such perfusion data fully requires information about the Na, K, and Ca levels actually attained, together with an estimate of pH.

Evidence from Measurement of Na and K in Relation to Blood Pressure

MEASUREMENT OF NA AND K IN CHRONIC HYPERTENSION OR HYPOTENSION. *Deoxycorticosterone (DCA) hypertension.* Ledingham (137, 138) studied the relation of Na and K partition to blood pressure in a series of

DCA-treated rats using inulin to estimate water distribution. Unfortunately, he analyzed only skeletal and cardiac muscle and hence his report of an absence of correlation must be treated cautiously. Despite his own rather negative conclusion, if we assume that his methods can only distinguish extremes and not transitional stages, his tables show several striking features. Blood pressure in the control-adrenalectomized group averaged 86 mm Hg, while the adrenalectomized saline-treated group reached 114 mm Hg. The two groups attaining the highest pressure were likewise adrenalectomized and received either DCA-saline or DCA-saline-cortisone and had average blood pressures of 191 and 221 mm Hg, respectively. Both Na_o and Na_i values were highest in these groups and the Na_o/Na_i gradients lowest. Again, K_o was lowest in both these groups, while K_i did not fit any pattern. The value for K_o is perhaps particularly important, since it has also been reported as a finding in the accelerated phase of essential hypertension in man (111, 131). Low levels of serum Na have also been noted at this stage of the disease (46).

Woodbury & Koch (211) also noted in the rat that DCA and aldosterone produce an increase in skeletal muscle Na which, judging by measurements of chloride space, is largely intracellular and represents an increase in Na_i . Potassium was little altered. Unfortunately, blood pressure was not measured. Ferrebee *et al.* (62), using more laborious techniques, had long ago shown that DCA in the dog caused a gain in Na_i at the expense of K_i . Cier and co-workers (29) and Gross & Schmidt (99) also claimed that DCA increases Na_i in skeletal muscle.

Insofar as blood pressure regulation is concerned it is more important to attempt to estimate the effect of DCA on Na and K in a representative of vascular tissue. The aorta has so far been the only tissue amenable to study and here, by and large, the evidence points the same way. The classic and most quoted paper in this field is that of Tobian & Binion (196), who reported an increase in both Na and K in the aorta of rats made hypertensive with DCA. From estimates of the extracellular space (based on chloride measurements) they believed that most of the increase represented a true intracellular gain. Tobian & Redleaf (199, 200) reaffirmed these findings in later studies.

Daniel & Dawkins (40) claimed that aorta electrolyte changes demonstrable in early DCA hypertension disappeared later in the disease. In early hypertension they noted a tendency for a gain in Na_i but, more

significantly, for K depletion in hypertensive rats under treatment compared with normotensive also under treatment. Most recently, Laszt (133) also reported a gain in aorta Na following DCA treatment.

By and large it would seem that DCA causes a gain in Na in both skeletal muscle and in aorta in the rat; a goodly part of this gain probably represents a true intracellular increase, but with the methods so far used it is difficult to assess just how much is actually intracellular. The gain in Na is apparently not accompanied by a parallel gain in water, so we are fairly safe in inferring from all authors that intracellular Na concentration, Na_i , is elevated. All reports uniformly fail to provide us, however, with simultaneous estimates of Na_i of the aorta and Na_o of the medium, which is a crucial piece of information. This same lack of information tends to nullify Laszt's claim (133) that blood pressure cannot be related to the total Na content of the aorta. In our opinion, it would be exceptional if blood pressure could indeed be related to one such simple parameter as that.

Other hypertensive states. We have considered DCA separately because of its obvious effects on electrolyte metabolism which might perhaps be considered to make it a special case. We turn now to a more general review of the findings for Na and K analysis in a divergent series of conditions united only by the fact that a sustained hypertension is a common feature.

Ledingham (139) has recently reviewed this and decided that the only common feature in these varied states is the elevated blood pressure itself. His negative view is based on his findings in hypertension induced by DCA, cortisone, renal artery constriction, and bilateral nephrectomy (136–138). As described above, he may have overemphasized the negative aspects of his data. It is unfortunate too that this conclusion should have been arrived at without any attempt to measure electrolytes and water in vascular tissue.

In their original report Tobian & Binion (196) considered renal as well as DCA hypertension in the rat. Aorta Na and K were both elevated following renal constriction in rats developing hypertension compared to animals remaining normotensive after the same operation. Tobian (192) extended this work by using a low sodium diet to control the blood pressure rise of animals with renal constriction and found the changes directly related to the presence or absence of hypertension.

More recently Tobian & Redleaf (200) found that rats with post-DCA sustained hypertension, with adrenal regeneration hypertension, and with the

hypertension that may persist after excision of an ischemic kidney all show an increase in aorta Na and K. This increase seemed to them to represent a true gain in Na_i and K_i . There is a suggestion that these studies may be pertinent to the problem of hypertension in man, for Tobian & Binion (195) found an increase of both Na and water in the renal arteries of human hypertensives. Na was increased more than water, but the technique used cannot distinguish intracellular from extracellular locations. Not too much weight should be given this type of study, however, for as all workers in the field know, electrolytes may exchange rapidly across vessel walls both immediately preceding and certainly after death.

In general, experiments in many laboratories support the thesis that Na and K in tissues are altered in hypertension, but the emphasis shifts now to the one, now to the other. Thus, Eichelberger (53) long ago measured an increase in Na and fall in K in the skeletal muscle of dogs made hypertensive by renal constriction. Assuming an extracellular position for chloride there appeared to be a true rise in Na_i and fall in K_i . Laramore & Grollman (132) found a general rise in tissue Na and water and a fall in K in the later stages of renal hypertension in the rat. Later, however, Grollman (96) found the same quantities unchanged in hypertension produced as a late sequela of choline deficiency. More recently Koletsky *et al.* (129) analyzed the mesenteric arteries of rats with acute renal hypertension and also found a gain in Na, K, chloride, and water. These authors, however, cautiously refrained from attempting to partition the electrolytes on the basis of chloride space.

In agreement with Tobian and associates, Freed *et al.* (70) found an elevation in aorta K in renal hypertensive rats but a less well-defined increase in Na. The reduction of the hypertension by dietary K deprivation was followed by a proportionate decrease in aorta K, and the return to hypertensive levels on refeeding K was accompanied by a return rise in aorta K. On examining the data, however, it is evident that the increase in aorta K occurs in rats with renal constriction whether or not the pressure goes up. This same inconsistency was noted by Tobian & Binion (196).

Laszt (133) does not find an increase in aorta Na at all consistent with the presence of hypertension in rats, but claims the rise of K to be so.

Houck (119) pointed out that dogs maintained in good balance for 5 to 111 days following bilateral nephrectomy show a gain in tissue Na and fall in K

despite relatively normal extracellular values. This apparently indicates an association of their sustained hypertension with an elevation of Na_i and fall in K_i . Greene & Sapirstein (95) found an increase in total body Na in rats made hypertensive by subtotal nephrectomy. Haight & Weller (103) studied rats made hypertensive by chronic high salt feeding; they found hypernatremia and an increase in skeletal and heart muscle Na and K especially pronounced in the hypertensive rats but no conspicuous differences in aorta electrolytes.

Other sustained abnormal blood pressures. The regularly observed fall in blood pressure in Addison's disease or following adrenalectomy requires no comment. Among other phenomena, it is associated with a reduction of tissue Na from both intracellular and extracellular compartments (30, 52).

Freed *et al.* (69) examined the relation of plasma to aorta Na and K in rats made hypotensive by K deprivation. Both Na and K declined in plasma as well as in the aorta, although the authors stress only the change in K. Tobian (191) found that rats on a low Na diet lose a sizeable amount of aorta Na, while serum Na may actually rise a little. Although blood pressure was not measured it was assumed to tend toward lower values.

Trauma may lead to a "posttraumatic sodium-potassium shift" during which plasma Na falls and K rises. This is associated with hypotension (186).

MEASUREMENT OF Na AND K IN ACUTE HYPERTENSION OR HYPOTENSION. Although investigation of the association between acute changes in blood pressure and electrolyte exchanges is comparatively recent, the findings are more clear-cut than any we have so far considered. The independent findings from different laboratories all fit together nicely even though interpretations vary. Since this approach bears directly on the relation of ions to vascular smooth muscle tension, the facts obtained must form the basis of all theoretical discussion. Accordingly, we shall present these facts in some detail.

Perhaps the earliest report of a relation between ionic concentration in the serum and a pressor agent was that of D'Silva (50) in 1934. He reported that, in the cat, following the intravenous injection of 50 μg of epinephrine or 10 units of Pitressin intravenously serum K rose sharply as much as 3 meq per liter within 1 min. Since these massive doses of the order of 10 μg per kg epinephrine and 2 units of Pitressin per kg also caused a rise in blood sugar, this author related the K rise to the glycogenolytic effect

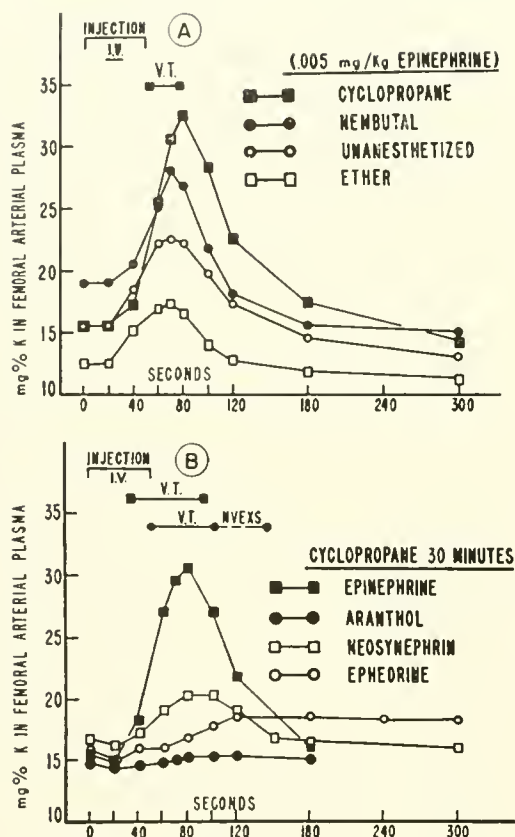


FIG. 6. *A*: influence of anesthesia on plasma $[K^+]$ rise induced by epinephrine in the dog. Arrhythmias and time of their occurrence shown by horizontal lines at top of figure. *I.T.* = ventricular tachycardia. *B*: effect of a series of sympathomimetic amines on plasma $[K^+]$ in the dog. *I.T.* = ventricular tachycardia, *V.E.X.S.* = numerous ventricular extrasystoles. [From O'Brien *et al.* (155).]

of the injections rather than to the blood pressure effect. This explanation for the rise of K remained unchallenged and uncritically accepted for almost two decades.

O'Brien *et al.* (155) in 1953 obtained beautiful curves showing the rise of plasma K after rather lower doses of norepinephrine, 5 μ g per kg, in dogs. Although norepinephrine does not have any marked effect on the mobilization of glucose and although these authors pointed out that it is blocked by Dibenamine, which would not block a glycogenolytic effect, the original explanation still persisted. O'Brien and his associates also pointed out that the choice of anesthetic modified the effects, ether being the worst for blurring the effect, cyclopropane affecting it least, Nembutal almost as good as cyclopropane. These important observations were unfortunately ignored by most later workers including ourselves. (In our more

recent studies we have found the effects considerably sharpened if a barbiturate mixture is used instead of ether.)

Muirhead *et al.* (153) in the next year restudied the problem. They gave norepinephrine by infusion in total doses of 1 to 7 mg per kg in 50 to 180 ml of saline over periods ranging from 20 to 50 min. Concerning their results they wrote: "In many of the experiments the sodium curve represents an approximate mirror image of the blood pressure curve. In most of the experiments the changes of potassium were not as pronounced as those of sodium. In addition there seemed to be little if any correlation between blood pressure and plasma potassium. The latter is in contrast to the variations in sodium levels which reflected even sudden changes in blood pressure." No real change in radiosulfate space or in chloride concentration was observed. These observations did not have the impact they ought to have had for the doses used were very large.

Tobian & Fox (197) then approached the problem directly and analyzed segments of dog femoral artery before and after infusing norepinephrine sufficient to maintain a blood pressure elevation for 30 min. A consistent fall in artery K and a less consistent gain in Na was observed. These changes were believed to represent a fall in K_i and rise in Na_i , but the authors tended to underestimate the importance of the Na change since it was less consistent. In our view, the difficulties inherent in such tissue analysis and their basic range of error make it highly significant that even this trend for a sodium increase was observed; in fact, a sizeable Na gain was found in 9 of 12 dogs. In the light of later evidence, we must conclude that a fall in K_i and a real gain in Na_i , probably with water, actually did occur.

Shortly thereafter, following up the possibility that Pitressin might have an extrarenal action, we observed that this agent caused a shift of water out of the extracellular space in the bilaterally nephrectomized rat. In a more detailed study, we found that Na also left the extracellular space in association with, but in excess of, water so that there was a measurable fall in plasma Na concentration (82). The relation of dose to response was presented at this time and the correlation of the shifts with blood pressure noted. In interpreting these exchanges of salt and water, we took into account the changes which other workers had previously observed to follow norepinephrine administration and hypothesized that both sets of observations could be related by a general rule that blood pressure regulation depends on the

sodium transfer systems, broadly defined. The rise in plasma K following Pitressin administration was considered an integral part of the phenomenon, but left aside from this first theoretical approximation for later consideration.

In these first studies we overestimated the absolute magnitude of the water shift that follows Pitressin administration. This was corrected in subsequent studies. The effects of norepinephrine on Na, K, and inulin space in the nephrectomized rat were then compared with those produced by Pitressin and again a net loss of extracellular Na was observed in association with the blood pressure rise (75). Pitressin in the large doses used caused a measurable fall in plasma Na indicating that Na moved in excess of water. With the techniques at hand (flame photometry, arterial blood sampling) no clear fall in plasma Na concentration taken alone was observed with norepinephrine, but a shift of Na and water was claimed on the basis of replicate experiments in which extracellular sodium was calculated. Angiotensin was then compared with Pitressin in the nephrectomized rat (76). Both agents given intravenously produced a measurable fall in plasma Na concentration and a fall in extracellular fluid volume (inulin) associated with the rapid rise of blood pressure. While Pitressin produced a measurable increase in extracellular K, angiotensin did not.

It was clear at this time, at least for norepinephrine, that the fall in Na and water and the rise in K which we were measuring in the extracellular compartment of the rat corresponded qualitatively to the gain in Na and loss in K which Tobian & Fox (197) had measured in the femoral artery of the dog. Daniel *et al.* (41) then injected a pressor dose of norepinephrine within the physiological range, 1 μ g per kg, in the rat. They found that the aorta was rapidly depleted of K while Na tended to increase. This is surprisingly good confirmation in view of the fact that the Na shift is probably partly obscured by a movement of water which these workers could not measure.

Subsequently, this group (42) studied the effects of Pitressin and isoproterenol (isopropyl norepinephrine, a peripheral vasodilator) on aorta electrolytes in the rat. They concluded from the variations in aorta sodium that during blood pressure changes, Na moves into (rising blood pressure) and out of (falling blood pressure) vascular muscle cells. Since they were dealing with the aorta, an outward movement of K occurred only with those drugs known to cause an aorta strip to contract. They pointed out, however, that the total amount of Na which we had reported to

leave the extracellular space could not possibly be accommodated within the cells of the vascular tree. This difficulty has now been satisfactorily resolved by our observation that skeletal muscle also takes up sodium under the influence of Pitressin (85).

In the rat, studies of changes in plasma Na, K, and inulin space during changes in blood pressure are technically difficult, since each step in drug, dose, or time interval requires the use of separate groups of animals. To circumvent this, as well as to extend the observations to the dog, we studied the problem in the bilaterally nephrectomized dog using norepinephrine, isoproterenol, angiotensin, and Pitressin (73). We found that the calculated extracellular Na (product of inulin space and plasma Na) declined as pressure rose and increased as it fell; the two measurements consistently formed mirror images. Calculated extracellular K in general moved inversely to Na and hence in parallel with the pressure except in the case of angiotensin where, as in the rat, no K shift was found.

In the case of norepinephrine, the simple measurement of plasma Na was an inconsistent index of Na movement, since the real decrease in this ion is partially masked by a movement of water in the same direction. For the same reason, K concentration is a consistent but inaccurate estimate of K movement, since the change is magnified by inverse movement of water. In the case of Pitressin, although both Na and water move out of the extracellular compartment, the Na shift is well in excess of the water so that, if the dose is adequate, a fall in plasma Na is readily observed. These findings are remarkably similar to those obtained in the rat.

Warren (205) has recently studied the effect of Pitressin on Na, K, and inulin space in the trained, conscious, intact dog. He observed similar exchanges to those previously reported in the nephrectomized dog even though he used considerably smaller doses of Pitressin (30 mU/kg as a single i.v. injection versus 200 mU/kg/min for 10 min by infusion).

Recently the Na and K electrodes have been applied to this problem. In the first experiments we used only a sodium electrode interposed into the femoral artery of the dog (80). The aim was to determine whether pressor and depressor agents actually shift Na levels as blood sampling procedures indicated. The result was unequivocal; the pressor response to norepinephrine, epinephrine, and angiotensin was regularly accompanied by a fall in electrode potential indicating a fall in sodium concentration, or more precisely, sodium activity. In terms of degree of change, time course, and duration of effect, each agent

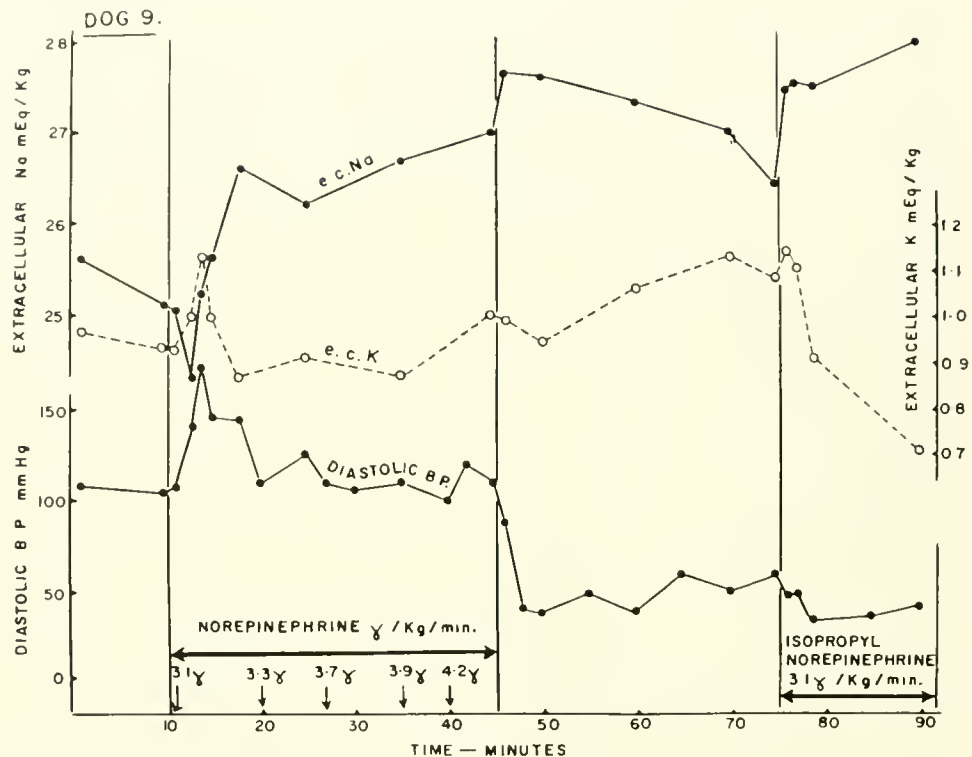


FIG. 7. Changes in extracellular Na and K associated with blood pressure changes in the dog.
[From Friedman *et al.* (73).]

produced its own characteristic pattern. The depressor response to acetylcholine, histamine, and isoproterenol was accompanied by oscillations in the tracing which tended to be inverse to those observed with pressor agents. Later, in a similar arrangement using two electrodes, norepinephrine was shown to produce a rise in (K^+) inverse to the fall in (Na^+) (81).

The technique for electrode monitoring of (Na^+) and (K^+) in flowing blood was then modified after Haddy so as to control flow rate through the electrode as well as through the vasculature of the limb (122). The femoral artery of the dog was interrupted by a length of polyethylene fed through a Sigmamotor pump. The femoral vein was similarly lengthened and passed through a smaller division of the pump. The venous outflow passed through Na and K cannula electrodes in a shielded enclosure. This arrangement ensured not only a constant limb inflow but also the passing of a proportion of the venous outflow at a constant rate past the electrodes. Quantitative measurements could also be made, since calibrating solutions could be injected into the venous tubing proximal to the pump. One pressure transducer was inserted on the arterial side between pump and limb and another into a brachial artery. Small amounts of

vasoactive agents sufficient only to activate the limb vasculature without producing any noticeable systemic effects were used.

In general, limb vasoconstriction induced by norepinephrine or epinephrine was associated with a fall in blood (Na^+) and often with a rise of (K^+). Larger doses tended to produce a biphasic response in (Na^+), that is, an initial transient rise preceding the fall. Vasoconstriction produced by serotonin or angiotensin was associated with similar (Na^+) change unaccompanied by any consistent (K^+) deflection. Vasoconstriction produced by Pitressin was associated with a fall in (Na^+) and consistent rise in (K^+), both noticeably greater in degree and duration than with other agents producing an equal degree of vasoconstriction. Limb vasodilatation induced by isoproterenol, acetylcholine, or histamine was accompanied by a rise in blood (Na^+) without any consistent change in (K^+).

A full analysis of rates and relations of ion and water movement is clearly required. For the moment, we may conclude that the movements of Na and K associated with changes in blood pressure reflect changes in tension in the peripheral blood vessels.

Only one report disturbs the general consistency of this phase of the investigation. Headings *et al.* (109)

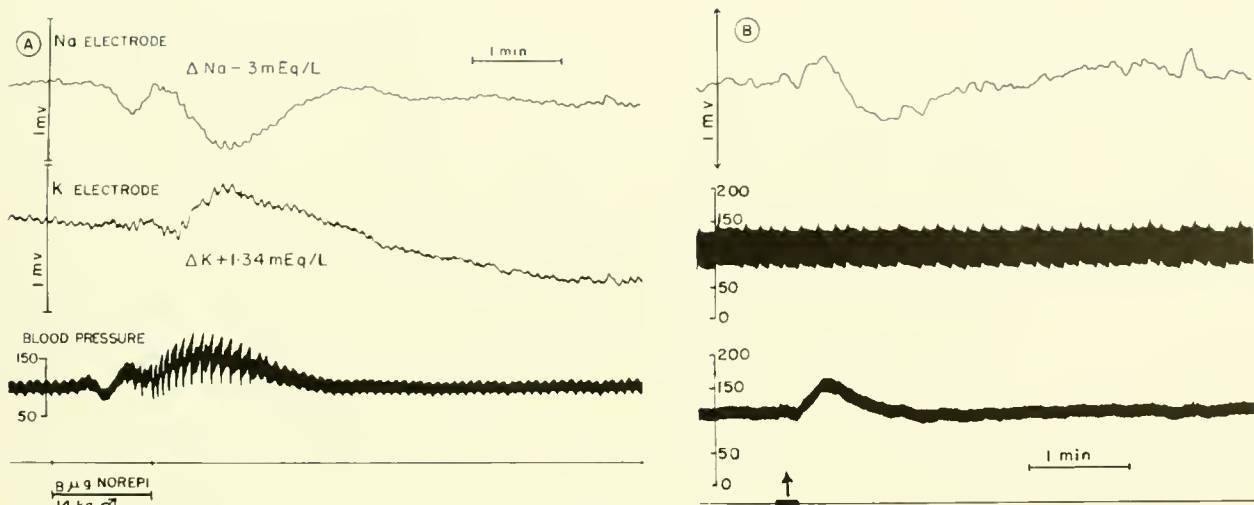


FIG. 8. Changes in blood (Na^+) and (K^+) monitored with the Na electrode ($\text{Na}/\text{K} = 250/1$) and K electrode ($\text{K}/\text{Na} = 5/1$) in the dog during A, systemic blood pressure rise induced with norepinephrine and B, limb pressure rise induced with norepinephrine. [A, from Friedman *et al.* (81).]

found that dog carotid artery rings stimulated electrically gained Na and lost K. Epinephrine, however, in an amount sufficient to produce the same contractile response did not produce these changes.

We may conclude that, in general, an acute increase in tension of vascular smooth muscle is associated with a gain in Na_i and a gain in water. There is a strong suggestion that in some instances, at least, the gain in water may overshadow the gain in Na and may also anticipate it. A loss in K from cells to environment is almost always observed. Similar ionic exchanges have been observed both in taenia coli and uterus during activity (16, 124).

These experiments give no information regarding the time relations connecting these phenomena nor do they suggest which event is cause and which is effect.

Evidence from Studies of the Relation of Electrical Activity to Tension in Vascular or Analogous Tissues

Bacq & Monnier (7) studied the relation of electrical activity to tension in a variety of smooth muscles obtained from the cat. They claimed that the laws common to all excitable tissues apply to smooth muscle as well. In their view the response to every excitation, in this case contraction or increase in tone, no matter how produced, is accompanied by a decrease in polarization. They considered the change in polarization to be the cause of the change in tonus. In accordance with theories current at that time de-

polarization was attributed to the exit of K^+ from cells.

Although Bozler (17) carried out the first basic studies of electrical activity in smooth muscle using modern techniques it remained for Bülbring and her associates to carry out the difficult task of defining the ionic basis of that activity. In 1954 data were presented for guinea pig taenia coli suggesting that tension is inversely, and spike frequency directly, related to the membrane potential (19).

We can summarize these first experiments in a simplified form. A resting membrane potential of $60 \pm 9 \text{ mV}$ fell to 43 ± 10 and spike frequency increased when the tissue was stretched (increased tension). Histamine induced a fall in potential from 58 to 40 mV while tension and spike frequency increased. Epinephrine induced an increase in potential and a decrease in tension and spike frequency. Acetylcholine caused a fall in potential and increase in spike frequency and tension. Shortly thereafter Bülbring (20) reported that the increase in rate of spike discharge was proportional to the increase in tension. Then, in 1955 (21), fluctuations in membrane potential were observed to be related to the spontaneous rhythm of the taenia coli strip and periods of depolarization associated with increased tension and increased rate of spike discharge alternated with periods of repolarization, reduced spike frequency, and lower tension.

From this basis Born & Bülbring (16) then proceeded to the still more difficult technical problem of

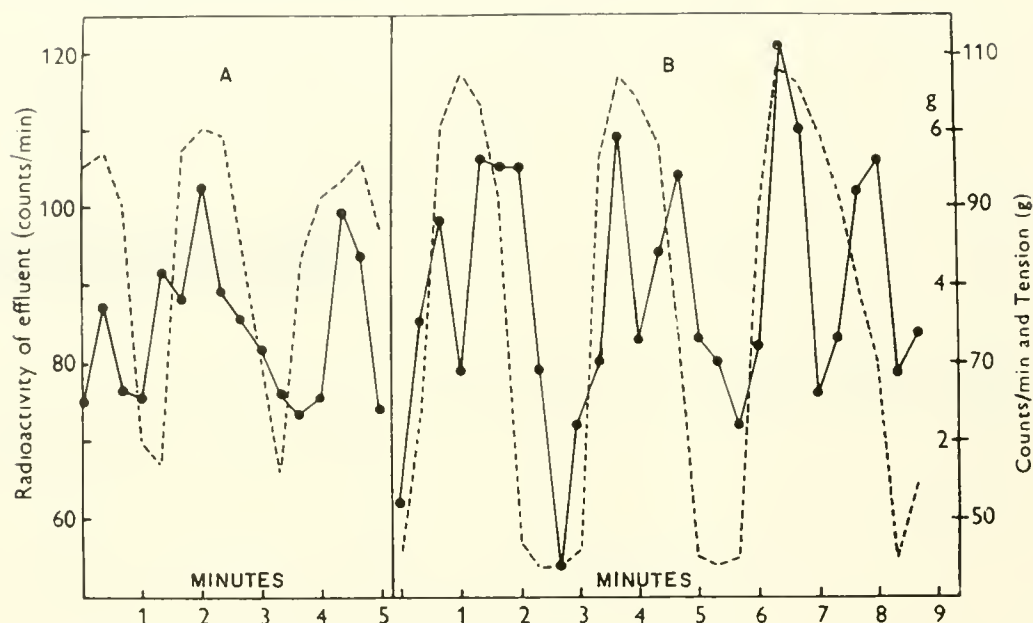


FIG. 9. Fluctuations of tension (*broken line*) and of radioactivity (K^{42}) appearing in washing solution (*continuous line*) of taenia coli during spontaneous activity *A*, before, *B*, in the presence of atropine 2×10^{-6} . [From Born & Bülbring (16).]

adding measurements of ionic exchange to the simultaneous monitoring of tension and electrical activity. By restricting their attempt to the simpler problem of measuring only K they succeeded quite elegantly and in so doing proved beyond doubt that basic ionic theory is generally valid, at least for the gut strip. They used K^{42} as tracer and analyzed the medium flowing past the tissue. Spontaneous activity was characterized by the parallel rise and fall of K efflux and tension so that as tension rose, K efflux increased and as tension fell, K efflux decreased. Similarly, histamine and acetylcholine produced contraction associated with a parallel increase in K efflux. Epinephrine, which causes relaxation of this particular preparation, seemed to do so by increasing K influx. The fall in membrane potential previously observed to parallel the increase in tension was evidently associated with an ionic shift here measured as K efflux. Presumably, if it had been technically feasible to measure, a primary sodium influx would have been recorded.

Born (15) then turned to a study of some of the metabolic problems concerned with contraction in smooth muscle and for the first time we find a firm separation of the relatively rapid changes in tension from the maintained changes which we recognize as *tonus*. The position is best stated by the author: "The development of tension by smooth muscle involves two mechanisms. One mechanism is responsible for

the immediate rise in tension which occurs when the muscle is stimulated and this mechanism continues to function in anoxia and in the presence of 2:4 dinitrophenol. The other mechanism is responsible for the sustained tension which the muscle shows, both spontaneously and following stimulation. This mechanism is abolished when metabolism is interfered with, e.g., by depriving the muscle of glucose or of oxygen, or by exposing it to 2:4 dinitrophenol."

Later studies of electrical activity have rather tended to cloud the picture. Bülbring & Lüllman (22) demonstrated that spike frequency and tension could be dissociated. Using dinitrophenol they showed that spike frequency could be made to increase or decrease without particular reference to tension changes. The inverse relation of tension to membrane potential still held under these circumstances, however, so that at this point we might tend to disregard spike activity. This idea is reinforced by Holman's observation (117) that the addition of KCl to the medium bathing a taenia coli strip increases tension and decreases the membrane potential. Further, at concentrations above 20 meq per liter, the relation of K_o to membrane potential is linear with a 33 mv slope per log unit change, an important fit with ionic theory although the low slope remains to be accounted for.

Burnstock & Straub (26) using an improved procedure, the sucrose-gap technique, verified the fact that K salts produced a membrane depolarization,

showed the importance of penetrability of the accompanying anion, and improved the relation of E_m to $\log K_o$ to yield a slope of 45 mv. This is still lower, however, than the ideal 58 mv which one would expect.

Holman (116) found more evidence to relate E_m and tension. She reported that raising Na_o to two or three times the normal level first increased tension and spike rate while reducing E_m . Later, as exposure was prolonged, the spikes disappeared although tension remained high and E_m low. These observations again argue for dissociation of spikes and tension, but later, Holman (118) took the position that spike frequency was an important factor in the development of tension and Axelsson (5) sustained this view.

The question of whether or not tension changes and electrical spikes are interdependent is of particular importance to our problem, since vascular tissue, so far as it has been studied, shows no spike activity whatever. Accordingly, tissues such as taenia coli are relevant only insofar as their tension may correlate with electrical activity other than that of a train of action potentials constituting the spike activity. Burnstock's recent study and argument is thus particularly important (24). He noted that smooth muscle of guinea pig taenia coli is relaxed by epinephrine and that this is associated with a rise in E_m and decrease of spike activity. The smooth muscle of the muscularis mucosa of the dog, by contrast, is contracted by epinephrine and in this case the epinephrine effect is associated with a fall in E_m and an increase in spike activity. It would therefore appear that at least for these types of visceral muscle both the membrane potential and the spike activity are correlated with tension. Under certain circumstances it is possible to dissociate the spike activity from the tension and the membrane potential alone then remains inversely correlated.

A similar situation arises in connection with studies of the uterus. The observation of Woodbury & McIntyre (212) that oxytocin, which contracts the pregnant uterus, reverses the membrane potentials of the single muscle cell is quite relevant for it again relates membrane potential to activity. On the other hand, the claim (43) that tension of the uterus strip is only correlated with spike activity suggests that this tissue is not analogous to vascular smooth muscle.

Electrical studies of vascular smooth muscle were almost nonexistent until very recently. Bozler (17) considered this type of muscle to be distinctive in being "multi-unit" unlike many other types which behave like single units. Recent detailed and elegant

studies by Burnstock & Prosser (25) and Prosser *et al.* (161) have placed this on a firmer footing. Vascular smooth muscle is here shown to consist of widely separated cells and its extracellular space calculated from electron microscopy is about 40 per cent of the total (see table 4). This contrasts strikingly with the other types of smooth muscle in which the extracellular space is estimated at less than 20 per cent. Vascular smooth muscle shows no conducted electrical activity and no spikes. Our theoretical discussion must reckon with these distinctive features.²

ROLE OF CALCIUM AND MAGNESIUM IN VASCULAR SMOOTH MUSCLE TENSION

Calcium

There is too little information concerning the detailed effects of calcium and magnesium on vascular tissue to permit any elaborate discussion. What little evidence we do have is fortunately consistent. The older literature has been reviewed by Evans (60). A much larger literature deals with the general direct involvement of calcium in the actomyosin system (51) and in the metabolic cycle of cells (141). We shall not develop this broad field of physiological chemistry, which would lead us far from our immediate subject, but we must note that calcium ions are evidently necessary for the contractile machinery to work.

The physiological implications of this have been demonstrated by Heilbrunn & Wiercinski (110). They showed that Ca in high dilution injected directly into the single skeletal muscle fiber caused an immediate and pronounced shortening. This effect is not shared by any other ion normally present in any quantity in muscle, but it is also produced by Ba. These authors, like others since (142), support the view that Ca links the ionic processes at the membrane to the contractile mechanism. This point obviously has as much importance for contraction and tonus in vascular as in any other muscle tissue.

In studies of intestinal segments there seems to be general agreement that the addition of Ca to the medium increases tone (189, 208). More important to our thesis is the demonstration that withdrawal of

² Recent successful impalement of single smooth muscle cells in turtle aorta and inferior vena cava segments has shown specialized types of action potential in association with tension changes. (Roddie, I. C. and S. Kirk. Transmembrane action potentials from smooth muscle in turtle arteries and veins. *Science* 134: 736, 1961.)

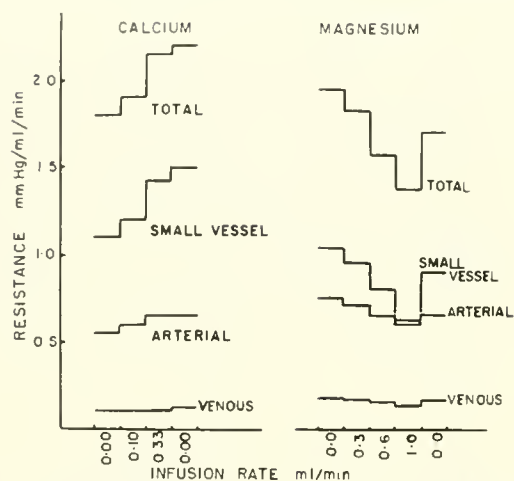


FIG. 10. Average effect of 10% CaCl_2 or 10% MgSO_4 infused into the brachial artery on dog forelimb vascular resistances. [Graph prepared from tabular data in Haddy (101).]

Ca from the medium causes a dissociation of the contractile mechanism from action potentials in the guinea pig taenia coli. From this, Axelsson & Bülbbring (6) have concluded that Ca is essential for the activation of the contractile mechanism by action potentials. Hurwitz *et al.* (121) have shown this in another equally direct way. They observed that prolonged exposure of the guinea pig ileum to a calcium-free environment divests the tissue of its ability to contract in the presence of an appropriate chemical stimulus. Further, the substitution of Mg for Ca in the medium accelerates the loss of contractility. Even so the membrane processes governing ionic exchanges still function so that a stimulus which no longer causes contraction will still cause K efflux.

Zsotér & Szabo (216) have reported that the feeding of a high calcium diet to rats for 10 to 15 weeks causes an increased sensitivity of the mesoappendix to the topical application of epinephrine. As we have discussed earlier, however, this type of result is difficult to interpret, since the variable (calcium feeding) is so remote from the target. Much more revealing is the observation of Haddy who showed that the infusion of hypertonic calcium salts caused constriction of all segments of the peripheral vascular bed of the dog forelimb under conditions of controlled flow (101). It will be recalled that hypertonic solutions in general produce vasodilatation so that the result with calcium is particularly striking. In a later study Overbeck & Haddy (156) reported that while the infusion of isotonic KCl produced peripheral vasodilatation, isotonic CaCl_2 caused vasoconstriction.

Woolley (213) has suggested that serotonin acts directly on the cell membrane to transfer calcium from the exterior to the interior of the cell. His evidence is quite incomplete, however, and a similar argument could be developed with equal reason to suggest that most if not all smooth muscle-contracting agents act through some similar mechanism involving calcium.

Magnesium

Haury (105) has clearly demonstrated that Mg relaxes bronchial smooth muscle and opposes the action of stimulating drugs. In well-controlled experiments in the dog and frog he found that small amounts of Mg given intravenously produced a blood pressure fall which was in large part due to peripheral vasodilatation (106). Schmid *et al.* (174) carried out a careful hemodynamic study in conscious dogs and also concluded that Mg salts produce peripheral vasodilatation as Hoff *et al.* (115) had earlier claimed. Stanbury (187) emphasized that the action of Mg is complex, since it produces changes in the autonomic nervous system and the heart as well as the peripheral vasculature. Zadina & Kriz (215) claimed that Mg had a direct relaxing effect on the isolated guinea pig intestine and depressed the response to stimulating agents.

Engbaek (59) reviewed the subject in 1952 and concluded that although it seemed reasonably certain that Mg ions acted to relax peripheral blood vessels this had not yet been shown to be a direct effect.

Pending any evidence to the contrary it seems reasonable to conclude, in summary, that Ca causes peripheral vasoconstriction and Mg relaxation. In general, these actions do not appear to be in any way specific to vascular smooth muscle. The special role of these bivalent metal ions in the chemistry of contractile protein may be involved and both ions, or at least Ca, may link membrane phenomena to the contractile mechanism.

ROLE OF H^+ AND OH^- IN VASCULAR SMOOTH MUSCLE TENSION

This subject is in a highly unsatisfactory state and permits no real conclusions other than that the pH of the medium is a most important variable, as we might have guessed. At this stage in the investigation of ions most workers are more concerned with maintaining

pH as an invariant than with noting and interpreting the effects of changes.

Schuler (177) measured the tension of mesenteric and phrenic artery rings while shifting pH to either side of normal. He found that tonus increased in both cases. Tobian *et al.* (198), using the spiral aorta strip of the rat, found that the contractile response to norepinephrine was maximal at relatively higher pH and minimal at lower. It seems to us that nowhere is the duration of immersion or exposure to the altered environment more important than in studies of the effect of H ions. Reference to table 2 will remind us of the extremely high mobility of H^+ and the ease with which it penetrates the membrane.

Rogers & Fenn (166) have shown that H^+ added to the medium exchanges rapidly with K^+ and Na^+ of cells. More recently, Saunders *et al.* (173) have also shown a partial replacement of K_i^+ with H_i^+ during dietary potassium depletion. At equilibrium, then, an original alteration in medium pH is replaced by an altered Na^+ and K^+ distribution. Duration of exposure must then be a critical variable. With this in mind, we can now examine the findings of workers using *in vivo* preparations. Technically, all the procedures to be quoted are beyond reproach as far as they go.

Burget & Visscher (23) showed a nice decrease in epinephrine response of the pithed cat proportionate to a stepwise fall in pH. This accords with Tobian *et al.* (198). Fleisch *et al.* (63) used good techniques to measure flow and pressure and found that a fall in pH of as little as 0.05 caused generalized vasodilatation.

More recent studies using the technique of controlled perfusion of a vascular bed are conflicting. Deal & Green (45), like Kester *et al.* (127) earlier, reported that solutions on the acid or alkaline side of physiological neutrality increased blood flow to limb muscles, indicating peripheral vascular relaxation. Skin vessels, however, showed a decrease in resistance as pH fell and an increase as pH rose. Fleishman *et al.* (64) showed that the picture is complicated by the fact that small vessel segments constitute independent resistances the magnitudes of which may actively vary in opposite directions. The net effects were dilatation of small vessels with an acute fall in pH and constriction with a rise in pH. Emanuel *et al.* (57) also reported that an acute rise in pH caused an increased peripheral vascular resistance through the renal vascular bed.

Clearly, we are in no position yet to draw any sort of general conclusions except that H ion effects are interwoven with those of Na^+ and K^+ .

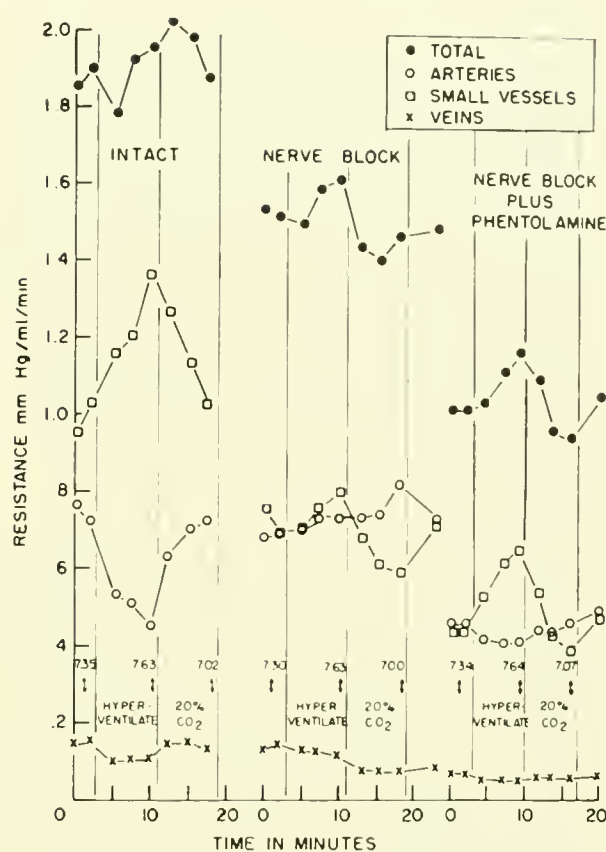


FIG. 11. Average effects of pH change upon total and segmental vascular resistances in the nerve intact, nerve blocked, and nerve blocked phentolamine dog forelimb. [From Fleishman *et al.* (64).]

ROLE OF ANIONS IN VASCULAR SMOOTH MUSCLE TENSION

There is a great need for systematic study in this field. So far, although anions have been considered from time to time, they have been studied only to underline the effect of their associated cations. No approach to this problem will really make much sense, however, until an acceptable basic model for the role of cations in the regulation of vascular tension is presented. This model need not be the final one as long as it provides a good rational framework. We hope to present such an integrated view in the theoretical discussion to follow.

THEORETICAL INTERPRETATIONS

A rational theoretical interpretation of the available evidence is now quite possible and has been attempted

by several workers. Raab (162) has suggested that the amount of sodium in the smooth muscle cell determines its responsiveness to catecholamines which he considers important in the pathogenesis of hypertensive states. Tobian & Redleaf (200) suggest that the amount of both sodium and potassium increases in the vascular smooth muscle cell in chronic hypertension and, by osmotic attraction, causes cell swelling and water logging. Tobian has recently reviewed this position (193, 194). We have presented the theory that the sodium transfer systems, broadly defined, and expressed in the sodium gradient, determine vascular tone (78). Raab (163) has recently revised his position to incorporate the sodium gradient into his basic thesis of catecholamine sensitivity.

Insofar as the cell is concerned, neither the amount nor the concentration of Na or K enclosed by its membrane has any meaning apart from their relation to the external environment as the gradients Na_o/Na_i and K_o/K_i . An increase in Na_i , for example, attracts water into the cell until osmotic equilibrium is established only if Na_i has increased relative to Na_o . Again, an increase in K_o will redistribute itself so as to produce no osmotic effect at equilibrium if Na_o/Na_i is kept constant. Or again, insofar as membrane potentials are concerned, an increase in K_i hyperpolarizes the cell only if K_o/K_i is made steeper thereby.

We need not belabor the point implicit in the basic principles of the introduction to this chapter but only urge that a satisfactory theory must be based on concentration (or activity) gradients and not stress either cell or environment alone in isolation. It is equally apparent from the evidence presented that a satisfactory theory must embrace both sodium and potassium. We believe that the following theoretical interpretation will fit many of the presently known facts and will perhaps serve to stimulate further thought. It will be presented in the form of generalizations with some supporting evidence. The remainder of the evidence is contained in the body of this chapter.

1) Vascular smooth muscle tension is inversely proportional to the membrane potential, that is, to the sum of the equilibrium potentials of Na^+ and K^+ where, in the basal state, the permeability of the cell to K^+ considerably exceeds its permeability to Na^+ . Laborit & Huguenard (130) and Furchgott (87) have already expressed this view.

The simple shift of water from cells to environment which can be induced by increasing the external tonicity will increase both Na_i and K_i , hyperpolarize the membrane and relax the cell. This explains the

vasodilatation which consistently follows the infusion of hyperosmotic solutions. Sustained exposure to hyperosmotic solutions containing particles other than Na^+ will not only lower Na_o but induce a flow of K^+ from cells to medium so that at equilibrium the membrane potential will be reduced and tension increased. This may explain postnephrectomy hypertension (83).

2) Acute change in vascular smooth muscle tension is ordinarily accomplished by agents which alter the permeability of the membrane to Na^+ . An agent which increases the permeability to Na^+ will produce an immediate depolarization and increase in tension followed by a flow of sodium from environment to cells. Such a flow of sodium has been consistently induced *in vivo* by all vasoconstrictors.

If cell volume is to be maintained unchanged during this process, potassium must leave the cell as sodium enters. The expected increase in K_o does not occur with all vasoconstrictors. In this case we must assume that some cell swelling occurs. Pending further data we recognize that real changes in cell volume may also be involved in changes of tension in vascular smooth muscle (65, 195).

3) Sustained change in vascular smooth muscle tension may be accomplished by agents which adjust and sustain the membrane permeability to Na. The equilibrium state for a given permeability is manifest in the Na gradient. Since the entrance and exit mechanisms for sodium are not necessarily the same (see Goldman equation) the same result can be achieved by varying either influx or efflux rate. The sodium gradient falls, for example, if influx rate is increased or efflux hindered. If Na_i tends to accumulate in a sustained manner due to either of these changes the cell can, within reason, compensate by increasing its work of extrusion. Presumably the first effort of the cell to compensate will be reflected by an increase in the cell machinery involved in the work of such Na extrusion. This capacity must, however, be limited so that equilibrium will next be attained at a lower gradient, that is, Na_i increases until equilibrium is re-established. The resultant accumulation of Na_i must lead to the extrusion of K_i , a new and lower membrane potential and an increase of tension.

We have described the evidence that Na_i is actually increased in sustained hypertensive states. It is equally clear that chronic sodium-depleting procedures tend to re-establish the basic normal situation. There is also good evidence that mineralocorticoids regulate the permeability of cell membranes to sodium (33, 74, 123). A control system which allows a small trickle of sodium to enter the cell and then

regulates the ease with which it is extruded permits very fine control of the sodium gradient.

4) The role of cell volume remains to be assessed both in acute and chronic changes of vascular smooth muscle tension. This is self-evident. We are repeating this point at this time to emphasize the fact that this problem cannot be dealt with properly until such time as water movements can be accurately measured (65, 195).

SUMMARY

The detailed supporting evidence leading to our final theoretical interpretation is contained in the body

of this chapter. In order to underline our intention we have referred briefly to some essential evidence which cannot be easily explained in any alternate way. It is our opinion that most of the apparently complex material presented can be temporarily but usefully rationalized by reference to the theory presented. It is allied with general ionic theory as it applies to other contractile elements (113) modified to serve the special needs of this particular tissue.

We conclude that vascular smooth muscle tension depends on ionic distributions and mobilities across the cell membrane. The transmembrane equilibration of both sodium and potassium has been stressed as has the possibility of a direct link with calcium.

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Lipid metabolism in relation to physiology and pathology of atherosclerosis

SAMI A. HASHIM

WILLIAM C. FELCH

THEODORE B. VAN ITALLIE

*Department of Medicine, St. Luke's Hospital, and Institute of
Nutrition Sciences, Columbia University, New York City*

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THE TERM "LIPID" enables us to assemble under one heading a number of organic substances which, although variable in chemical structure, are closely related in biological behavior. The physical and chemical processes by which a living organism operates are summarized by the term "metabolism."

Thus, lipid metabolism refers to the behavior in living organisms of fatty acids, their esters, certain hydrocarbons, phospholipids, and sterols. Recent technical advances permitting better separation, identification, and quantification of the various lipids have resulted in a vast store of new information about lipid metabolism. Much of this material still needs to be organized and evaluated in terms of its relevance to problems of human health.

"Atherosclerosis" (Gr. athero, mush) refers to a lesion of the arterial wall characterized, inter alia, by accumulation of lipid in the intima. The term was first suggested in 1904 by Marchand (144). Today atherosclerosis, by virtue of its deleterious effects on the various arteries of the heart, brain, and other important areas of the body, appears to be the major public health problem of Western man. Thus, by extension, lipid metabolism as it relates to the physiology and pathology of blood vessel walls has become a subject of vital importance.

The search for the etiology of atherosclerosis has included consideration of all elements in the classic epidemiologic triad—agent, host, and environment. Environmental factors have received special attention since evidence—epidemiologic, experimental, and clinical—has accumulated suggesting that dietary constituents and particularly dietary fats influence the development of atherosclerosis. Such evidence as applied to man necessarily has been indirect because of the inaccessibility of atherosclerotic lesions during life. It is now recognized that dietary constituents can profoundly influence lipid metabolism. The role

of diet-induced changes in serum lipids in the development of atherosclerosis has not been established. In man, atherogenesis appears to be a chronic process, requiring considerable time, perhaps years, to evolve. The disease can culminate in an acute obstructive event, frequently with disastrous consequences. At such a time a disturbance in the coagulability of the blood may occur resulting in the formation of an arterial thrombus. Thus, attempts have been made to correlate changes in serum lipids as influenced by diet with the development not only of atherosclerosis but also of a more acute change in coagulability of the blood.

The clinical sequelae of atherosclerosis, ischemia, and infarction of the heart, brain, and other tissues, have been carefully documented for years. Also, the gross pathologic processes, such as lumen encroachment, fibrosis, ulceration, calcification, and thrombosis, which underlie these clinical events have been understood by pathologists since the time of Virchow. Moreover, a reasonable explanation for the pathogenesis of the disease was advanced more than half a century ago and has not been disproved. Yet from the standpoint of etiology and intimate pathogenesis the basic nature of the disease remains obscure and debatable.

PATHOLOGY

The pathologic entity atherosclerosis must be distinguished from other blood vessel lesions, some of which have been previously lumped together with atherosclerosis under the generic designation, arteriosclerosis. Monckeberg's medial sclerosis differs pathologically, pathogenetically, and clinically from atherosclerosis. Various inflammatory lesions of blood vessel walls also can be sharply separated, although the generally held concept that thromboangiitis obliterans is an entity different from peripheral atherosclerosis recently has been questioned (209).

Another important consideration is that common textbook descriptions of atherosclerosis may in fact describe mostly complications or sequelae of an initial, clinically silent process that may start in infancy. Thus, lumen encroachment, fibrosis, calcification, ulceration, hemorrhage, and thrombosis are all late conditions.

What then is the initial lesion? What is the pathologic essence of the disease? The answer to these questions necessarily involves consideration of pathogenesis (to be discussed later) as well as descriptive

pathology. Fortunately, precise studies of early gross and microscopic lesions from human and experimental material are available (21, 55, 108, 109, 130, 162). The first gross lesion, often visible in infants, is the fatty streak, a linear yellow elevation usually found in the aorta. Microscopic examination of such a streak reveals underneath the heaped-up intima an accumulation of lipophages, cells which show a foamy, reticular cytoplasm with ordinary stains containing lipid solvents, but which are found, with appropriate fat stains, to be packed with lipid. Lipid is also found lying free between the lipophages. Whether the lipid which makes up the fatty streak is first intracellular or extracellular is as yet unknown. With larger lesions, lipid is also found below the internal elastic lamella in the media, but the smallest, earliest, grossly invisible lesions consist of a few foam cells lying directly under the endothelial surface of the intima. Thus, the lipid-containing foam cell is usually considered to be the earliest recognizable unit of the atherosclerotic process.

However, careful microscopic studies show other subtle anatomic changes (39, 126, 195) occurring *pari passu* with the appearance of lipid in the blood vessel wall. Elastic tissue stains reveal stretching and fragmentation of elastic fibers in the intima as an early feature. Other special stains show metachromatic changes in the ground substance of the arterial wall, and chemical studies have demonstrated mucopolysaccharide accumulations that occur along with, or possibly before, the appearance of visible lipid. An abundance of evidence, clinical and experimental, has shown that preceding damage to the arterial wall, toxic, infectious, chemical or physical, will accelerate and will influence the site of the atherosclerotic process. These findings have given rise to the theory that subtle, perhaps submicroscopic, alterations in the physicochemical state of the arterial wall may actually precede the more gross lipid accumulations.

PATHOGENESIS

Since the earliest pathologic lesions are only adumbrative, even with modern histochemical techniques, it follows that the intimate pathogenesis of the atherosclerotic lesion also remains obscure. It is understandable that nineteenth century pathologists considered the disease a degenerative one, an inevitable concomitant of the aging process and a simple result of wear and tear on the arterial wall. Even when atherosclerosis was separated from other arte-

rial lesions, it must still have appeared to pathologists of that era to be another phenomenon of aging, found along with cataracts, osteoarthritis and wrinkled skin, and occurring with increasing frequency with advancing years.

The pendulum did not swing until Ignatowski (110) in 1908 succeeded, by administering lipid-rich foods to rabbits, in producing arterial lesions similar to those occurring spontaneously in human subjects. A few years later Anitschkow (10) demonstrated convincingly that cholesterol in the diet was the atherogenic factor in experimental rabbit atherosclerosis. Since that time, a large body of evidence has led away from the degenerative theory. Some of these evidences are: the finding at autopsy of an occasional octogenarian virtually free of arterial disease; the contrary finding of fatal atherosclerosis in soldiers in their twenties; the relative freedom from the disease of premenopausal women; the increased incidence at autopsy of atheromatous lesions in patients with diseases involving lipid abnormalities such as diabetes, hypothyroidism, and other processes associated with hypercholesteremia and hyperlipidemia. Further information resulted from the epidemiologic finding of certain population groups relatively free of the disease at postmortem examination. Pathologists made further contributions to this change in concept by their studies in experimental animals; it is now recognized that, although man, certain other primates, birds, and swine are the only animals which seem regularly to acquire atherosclerosis spontaneously, there is a wide variety of species which can be caused to develop arterial lesions similar to those found in human material, providing only that appropriate experimental manipulations involving lipid metabolism are made.

All this pathologic evidence, along with a huge volume of clinical, epidemiologic, and biochemical studies, has led to the modern concept that atherosclerosis is potentially a preventable disease, a result of metabolic disorder rather than a degenerative process. This lipid concept of the pathogenesis of atherosclerosis can be stated in simple terms: man ingests an excess of lipid which overwhelms the mechanisms for its disposal; lipid then accumulates in the circulating blood and is deposited in the arterial wall.

How does this rather simple concept fit with the facts of the earliest recognizable pathologic lesion described above? At first glance, the fit seems perfect. An excess of lipoprotein material in the circulating blood filters through the endothelium of the arterial wall and is taken up there by tissue histiocytes to

form foam cells; the simple accumulation of these lipophages results in the gross arterial atheroma and sets off the chain of events leading to fibrosis, thrombosis, and the rest. Yet there are a number of questions which cast doubt on this simple hypothesis.

First, if the mechanism is merely one of filtration through the endothelium to the arterial intima, why are the anatomically similar veins not more susceptible to the atheromatous process? That intraluminal pressure plays some role is shown by the increased incidence of atherosclerosis in hypertensive patients, the occurrence of pulmonary artery atherosclerosis in individuals with pulmonary hypertension, and the finding of phlebosclerosis adjacent to arteriovenous fistulas.

Another disturbing question concerns the fact that the lipid deposit is not a universal arterial finding, coating the intima of the entire arterial tree, but rather a spotty, localized one, involving certain segments of certain arteries. A number of possible explanations for this finding have been offered. One argument is that localized changes in filtration pressure, occasioned by intraluminal physical forces such as whirlpool and eddy formation, determine the site at which lipid is deposited; the frequent occurrence of atheromatous lesions at bifurcations, branches and coarctations favors this theory (175). Another proposal relates the clinical predilection for thrombosis in atherosclerosis to its pathogenesis; the earliest lesion, by this concept, is a chance fibrin deposit on the endothelial surface, the spotty lipid lesion occurring secondarily to fibrin deposition (56). Another explanation depends on the clinical and experimental evidence that preceding arterial wall damage, physical, chemical, mechanical, or bacterial, will foster premature and extensive lipid deposits; by this theory, occult damage to the elastic tissue or ground substance (or both) of the arterial wall, from degenerative or extraneous cause, serves as the spotty focus for lipid deposit. Still another theory explains the spottiness on the basis of localized differences in various areas of the arterial wall, in the mechanisms for removal of lipid, either metabolic (enzyme overload), scavenging (number of histiocytes present) or anatomic (number of lymph channels present). Yet another hypothesis explains localization by denying filtration from the lumen; according to this concept, atheromatous lesions are preceded by a localized overproduction in the arterial wall of the lipids which make up the lesion (105). Sensitive radioactive tracer studies have indeed shown that arterial tissue can synthesize lipids, but recent reports (214) have indi-

cated that if any atheroma lipid comes from local synthesis, it is probably only the phospholipid component.

One other major question relating to the intimate pathogenesis of the atherosclerotic lesion remains unanswered: What are the mechanisms for incorporation of lipid into cells to form lipophages? In each of the hypotheses mentioned above for the pathologic background of the early lesion, the common hallmark, whether primary or secondary in time and in importance, is the lipophage or foam cell (156), the very name of which suggests incorporation of lipid (fig. 1). The knowledge of the exact derivation of the foam cell is fundamental to a better understanding of atherogenesis.

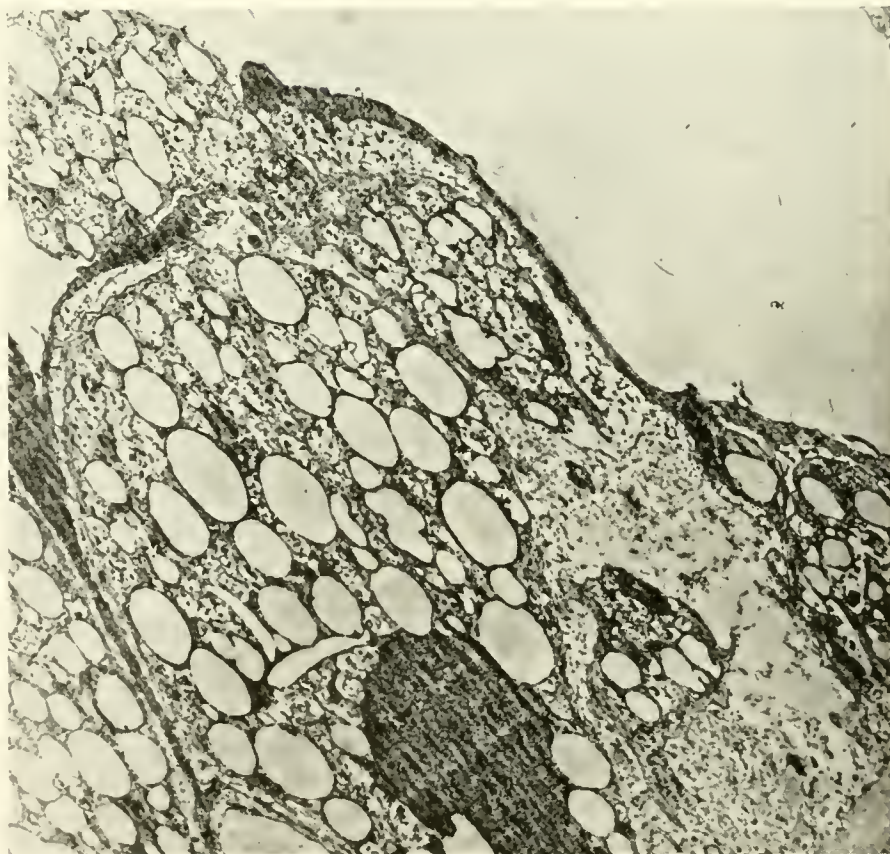
Is anabolic activity necessary for the accumulation of lipid in the cellular cytoplasm (as opposed to an engulfing mechanism)? One clue may be that the lipophage differs from the lipocyte, or adipose-tissue cell, by the former's higher content of protein and lipids other than neutral fat. Current attempts to study this problem by *in vitro* tissue culture techniques (180) may help to answer this and other

important questions about the role of the lipophage in atherogenesis.

Do lipophages form simply because there is lipid material available to be engulfed or phagocytized? In favor of this concept is the observation that lipophages are not peculiar to the atherosclerotic lesion; they are found as part of the detritus in hemorrhage into the various tissues; they are found as apparent scavengers in lipoid pneumonia; they occur in degenerating tumors; they are found experimentally after the subcutaneous injection of cholesterol suspensions; and they are found in the lipoidoses (Niemann-Pick, etc.) in massive accumulations involving the reticuloendothelial system. In most, if not all, of these situations, it is reasonable to assume that a scavenging attempt to rid the tissue of a local excess of lipid is involved.

Yet, in the atheromatous lesion, there appears to be an additional element—one of accumulation. A single minute atheroma, invisible to the naked eye, is made up of a tremendous number of lipophages, packed together in the subintima in such volume as to displace adjacent normal tissue and to project into

FIG. 1. Photomicrograph of a foam cell protruding from the subendothelial space of a rat aorta. $\times 8,400$. (Courtesy of Robert M. O'Neal, Baylor University.)



the lumen. What the stimulus is to cause this proliferative (or accumulative) element is unknown; the answer to this question is vital to a proper understanding of the intimate pathogenesis of atherosclerosis.

In summary, the major facts concerning the pathology of atherosclerosis, particularly its grosser aspects and its sequelae, are well documented. Debate still exists, however, concerning the more subtle, microscopic manifestations of the early atheroma, particularly in regard to the primacy of lipid deposition.

After more than fifty years, the lipid theory, despite some unanswered questions, seems to be standing the test of time. It will not become a universally accepted theory until certain difficulties are overcome. The spotty localization of arterial lesions, the mechanism of incorporation of lipid into tissue cells, and the stimulus to cellular accumulation in atheromatous lesions all are unsolved problems.

METABOLIC CONSEQUENCES OF INGESTION OF FOOD

Assimilation of foodstuffs is a condition of animal life. Yet food is never deposited unchanged. For absorption to take place, foodstuffs must be split, and far-reaching chemical transformations follow the absorption of digested food. The transformed food may be oxidized for the immediate production of energy or stored for short or long periods, depending on the needs of the body. With the exception of certain essential nutrients, the body is able to synthesize, interconvert, store, and mobilize its constituents.

When an individual ingests an assimilable carbohydrate, practically all of it is absorbed from the digestive tract and eventually reaches the liver as hexose. Part of the hexose is converted to liver glycogen; part is released into the circulation to be distributed to extrahepatic tissues; part enters muscle, where it is either burned or stored as glycogen. Once glucose enters muscle, becoming phosphorylated, it can no longer leave as such. One of its breakdown products, lactic acid, can diffuse out of muscle cells and re-enter the circulation. The adipose cells transform glucose into fatty acids, which are esterified with α -glycerophosphate to form triglyceride and are stored in this form. Glucose products, by a process of transamination, can be converted into amino acids.

Protein must be hydrolyzed into amino acids prior to absorption. Subsequently the amino acids can be

rebuilt by the body into new protein. Some of the amino acids can be converted to carbohydrate and thence to fat. Their carbon skeletons also are available for oxidation.

Following digestion, fatty acids passing through the intestinal mucosa are incorporated into very low-density lipoproteins (chylomicrons); these "molecules" are distributed in the systemic circulation to be disposed of by hydrolysis, oxidation, interconversion (but not into carbohydrate), or storage in various tissues.

Thus, carbohydrate and protein can be converted to and stored in the body as fat.

Soon after a conventional meal has been consumed, changes in concentration of glucose, amino acids, and fat (chylomicrons) occur in the blood. These "primary" changes induce "secondary" changes in the metabolic state. Ingestion of fat is followed by a postprandial lipemia, which may last for many hours. Thus, to evaluate the serum lipids properly, it is important to obtain blood samples from subjects who are in the postabsorptive state.

DIET

The average American diet, according to a summary of the 1955 Household Food Consumption Survey conducted by the United States Department of Agriculture (65), derives 44 per cent of its caloric content from fat, 13 per cent from protein, and 43 per cent from carbohydrate. The survey made no deductions for food discarded. The breakdown of calories derived from fat was: 18.3 per cent from saturated fatty acids, 18.6 per cent from oleic acid, and 4.5 per cent from linoleic acid. As expected from such an extensive survey, there were some regional differences in types and quantities of food consumed.

Knowledge of the chemical composition of natural fats remains incomplete, although great strides forward are being made. It is generally agreed that most natural fats, whether animal or vegetable, contain about 98 to 99 per cent triglycerides. The remaining 1 or 2 per cent includes diglycerides, monoglycerides, free fatty acids, phospholipids, and unsaponifiable sterols. Fatty acids comprise over 90 per cent of the triglycerides, with the remainder being glycerol. The naturally occurring triglycerides are mixtures varying widely in their patterns of fatty acids. The complexity of such glycerides is underlined

by the observation that at least 64 different fatty acids have been identified in butter fat (101).

In general, the degree of unsaturation of the fat depends upon the source of the fat. Fats of aquatic origin contain a wide range of unsaturated C_{16} , C_{18} , C_{20} , and C_{22} acids. Fats from land animals contain 25 to 30 per cent C_{16} , the remainder being mostly of the C_{18} series (102). The so-called essential fatty acids (mainly linoleic) apparently cannot be synthesized by animals, and must be obtained from the diet. The depot fat of certain animals, such as the pig, can be varied markedly in its content of linoleic acid, depending on the feed (60). Similarly, the adipose tissue fatty acids of man eventually reflect the dietary fatty acid pattern. This is true with respect to linoleic acid (103); but the medium chain fatty acids (C_{12} and below) have not been identified in the fat depots. Fats of vegetable origin vary tremendously in their pattern of fatty acids, as well as in their degree of unsaturation. For instance, coconut oil contains only a small quantity of linoleic acid, while safflower oil may contain 70 per cent or more. Dietary fats should not be described merely as "animal or vegetable," "saturated or unsaturated," but the actual composition in terms of fatty acids should be identified. Thus, when the effects of dietary fats on lipid metabolism are being evaluated, the specific fatty acids involved, their chain length, isomeric configuration, degree of unsaturation, and relative proportion in the diet must be considered.

Dietary phospholipids are found as complex mixtures in organ fats and certain raw vegetable fats, rather than in depot fats. Egg yolk is a rich source of phospholipid. As indicated by their name the phospholipids are a group of phosphorus-containing lipids; in addition, they contain a nitrogenous base. The lecithins, in which the base is choline, and the cephalins, in which the base is ethanolamine or serine, are classified as mono-amino-phosphatides. The component fatty acids are usually both saturated and unsaturated. The inositol phospholipid contains ethanolamine and tartaric acid. It is found in soybean phospholipids and in brain tissue. Other phospholipids include sphingomyelin, which is a diamino-phosphatide containing choline and sphingosine. Plasmalogens contain higher fatty aldehydes and ethanolamine (69). The complexity of dietary phospholipids is illustrated by their occurrence in egg yolk: 72.8 mols per cent phosphatidyl choline; 14.8 per cent phosphatidyl ethanolamine; 2.1 per cent lysophosphatidyl ethanolamine; 5.8 per cent sphingomyelin; 0.9 per cent plasmalogen; 0.6 per cent inositol

phospholipid; and 0.2 per cent phosphatidyl amine acids (169). One egg contains about 2 g of phospholipid.

The unsaponifiable fraction of food fats consists of sterols, including cholesterol (absent from vegetable fats), long-chain aliphatic alcohols, glycerol ethers, pigments, etc. Finally the fat-soluble vitamins, A, D, E, and K, may be found in this fraction.

FAT DIGESTION AND ABSORPTION

Generally speaking, lipids are not readily miscible in water. To be able to absorb, transport, and utilize fatty acids and other lipids, man has had to evolve rather elaborate mechanisms for making these water-immiscible or hydrophobic materials compatible with a system whose basic medium is water. The mechanisms used to deal with the water-insoluble lipids as they enter the body include hydrolysis, emulsification, chemical combinations with substances containing hydrophilic groups, and complex formation with substances conferring greater water miscibility and dispersibility, such as bile acids and proteins.

The mechanisms of digestion and absorption of dietary fat have been subjects of controversy for many decades. An early theory was proposed by Pflüger (161) who described dietary fats as being emulsified by bile salts in the small intestine. The triglycerides were then completely hydrolyzed by pancreatic lipase to fatty acids and soaps. Being water-soluble, these products were readily absorbed. However, it soon became apparent that intestinal pH is too low for fatty acids to exist as soaps. It also became apparent that the absorbed fat in lymph is mainly in triglyceride form. Thus, glyceride resynthesis by the intestinal mucosa was postulated. The modern concepts of fat absorption arise from Frazer's work (67, 68). It is now believed that hydrolysis of dietary glycerides need not be complete in order for absorption to occur.

Frazer's original "partition theory" (66) postulated that fatty acids passed directly into the portal circulation while the partial and unchanged triglycerides were somehow transported across the mucosa into lymph as chylomicrons. This theory has failed to survive in its original form as a result of more recent work (16, 145) including Frazer's own (70). Portal venous transport of fat is now known to occur only with fatty acids of less than ten carbons, which comprise less than 5 per cent of dietary fats.

The digestion and absorption of long-chain fats remain a subject of controversy. Frazer (70) has

cally normal men (38). In obese individuals the amount of body fat may reach 33 to 40 per cent of body weight.

During the past twenty years there has been an increasing awareness that adipose tissue is a dynamic organ capable of responding to a variety of stimuli. The experiments of Schoenheimer (184) and others have shown that depot fat has a definite turnover. Its half-life in the rat has been estimated to be 6 to 8 days. In man, turnover of depot fat is much slower, with a half-life of many months, in the presence of adequate caloric intake. When the availability of carbohydrate is reduced, depot fat cells can quickly mobilize free fatty acids which are then bound to albumin and carried in the blood to muscle, liver, and other tissues (52, 84).

The relationship between the availability of carbohydrate and the rate at which fatty acids are mobilized from depot fat is important. Breakdown of glucose through the Embden-Myerhof pathway and the hexosephosphate shunt may provide certain cofactors necessary for fatty acid synthesis (lipogenesis). Insulin promotes entry of glucose into the cell and thereby provides a stimulus for further metabolism of this hexose. Fatty acid synthesis appears to be somehow dependent on the rate of glycolysis. In diabetes mellitus glycolysis is depressed because of insulin lack; in addition, the rate of fatty acid synthesis is greatly suppressed. At the same time, the rate of hydrolysis of depot fat increases, and the resultant fatty acids are carried into the circulation as free fatty acids. For example, in uncontrolled diabetes, enormous amounts of fat can be mobilized, leading to fatty liver, hypertriglyceridemia, and hyperketonemia. Administration of insulin corrects the situation in a manner that has not been elucidated (203), but probably relates to the ability of insulin to reduce the rate of fatty acid mobilization from adipose tissue.

Hormonal Influences on Adipose Tissue

In addition to insulin, several other hormones have been found to influence lipid mobilization. It is emphasized that hormones do not initiate events within cells, but merely regulate the rate at which some of these events occur. Early studies (148) indicated that when large doses of posterior pituitary extract were injected into rats or rabbits there resulted an accumulation of fat in the liver. Similarly, an increase in liver fat and a decrease of carcass fat of the rat were found following the injection of anterior pituitary extract (19). There have been recent reports

that a posterior pituitary component, a relatively small polypeptide, has a potent mobilizing effect on omental and mesenteric fat in animals and man (185, 213). As yet there have been no reports on the influence of this posterior pituitary material on mobilization of free fatty acids (95). In contrast, it was found (177) that the injection into rabbits of crude extracts of whole or anterior pituitary gland of hogs, sheep, cattle, or man induced visible lipemia which was considerably greater than that induced by recognized anterior pituitary hormones. Thus it was suggested that the lipemia-producing principle might be an independent hormone, or that the lipemia was the result of synergistic action of known hormones, although the lipemia-producing anterior pituitary component apparently contains negligible or undetectable amounts of eight known pituitary hormones (178). Also, following injection of this material into rabbits, there was a rapid and enormous (tenfold) increase in free fatty acid levels. This was followed within 12 hours by a twofold to fivefold increase in serum total lipid concentration, including significant increases in the serum levels of triglycerides, cholesterol, and phospholipid. It is difficult to ascertain from these studies whether or not the lipemia that was produced was mediated through another gland, since the recipient animals were neither hypophysectomized nor adrenalectomized. The authors have explained their results by postulating that the active principle mobilizes free fatty acids from depot fat. The increase in triglyceride, cholesterol, and phospholipid in serum is believed due to increased rate of formation of these substances in the liver, in response to increased hepatic uptake of free fatty acids.

The possibility that there may be two new factors capable of mobilizing depot fat, one from the anterior and one from the posterior pituitary, deserves further exploration and confirmation by other investigators.

Of the known pituitary hormones, growth hormone has been shown to possess free fatty acid-mobilizing properties in the intact organism (168). Growth hormone action on depot fat (and other sites) appears to depend upon the phylogenetic relationship of the recipient animal to the donor source. For example, beef growth hormone mobilizes fat in cattle and in the rat but not in monkeys or human subjects. Knobil (125) has shown that the administration of growth hormone stimulates, while hypophysectomy inhibits, free fatty acid release from the epididymal fat body of rats. The manner in which growth hormone promotes free fatty acid release has not been fully elucidated.

Adrenocorticotrophic hormone (ACTH) has been

found to be very active in inducing free fatty acid release from adipose tissue in vitro (43, 61). However, such an effect is not readily demonstrated in vivo. The reason for this discrepancy is not clear, although a difference in species response to ACTH with respect to free fatty acid release has been offered as a possible explanation (61).

The role of thyroid in the metabolism of depot fat also is under study. The lipolytic response of adipose tissue from thyroidectomized animals (which had been suppressed) was made normal by restoration of the euthyroid state, while hyperthyroidism accentuated such a response (170). Moreover, it has been shown that the treatment of hypothyroid patients with thyroid restored to normal their free fatty acid response to growth hormone (167). Thus the thyroid appears to play a permissive role in fat mobilization, potentiating the action of certain lipolytic agents.

The autonomic nervous system was long suspected of playing an important part in the metabolism of depot fat (24, 207). Early observations on the autonomic innervation of adipose tissue have received support from more recent studies on the action of epinephrine and norepinephrine on depot fat. Subcutaneous administration or intravenous infusion of epinephrine and norepinephrine induced significant elevations of free fatty acids in the plasma of intact animals and human subjects (52, 80, 84). Moreover, adipose tissue in vitro has been found to be exquisitely sensitive to epinephrine and norepinephrine in terms of free fatty acid release (27, 61, 137, 210). It has been shown that adipose tissue liberates glycerol in response to epinephrine and norepinephrine (61, 137) suggesting that the mode of action of these hormones on adipose tissue involves hydrolysis of triglyceride. An epinephrine-sensitive lipolytic system has been reported in adipose tissue (172). The influence on depot fat of chronic administration of epinephrine and norepinephrine, as well as other sympathomimetic agents, remains unknown.

The various factors influencing lipogenesis and mobilization of fat from adipose tissue are summarized in figure 3.

In view of the importance of the subject of lipid mobilization and lipogenesis in the scheme of knowledge about metabolism, it is surprising that investigation in this area has lagged until recently. Conceivably, as knowledge of the subject increases, the physician will be the beneficiary of valuable adjuncts in the treatment of lipid disorders. Thus, adipose tissue, once thought to be a relatively inert storehouse of dense calories, has been found capable of partaking

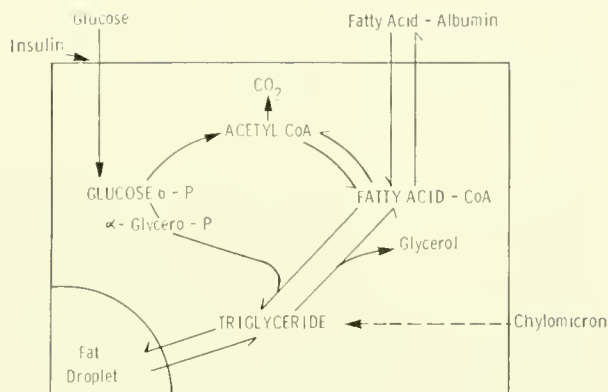


FIG. 3. A scheme of lipogenesis and lipolysis in the adipose cell. Free fatty acid release is promoted by: glucose lack, starvation, insulin lack, epinephrine, glucagon (in vitro), norepinephrine, growth hormone, ACTH (in vitro), thyroid hormone (? permissive), and certain extracts from anterior and posterior pituitary glands.

actively and rapidly in a number of metabolic processes and of responding to a variety of humoral and autonomic stimuli.

THE SERUM LIPIDS

The serum lipids can be broadly classified under two major headings: the lipoproteins and the free (or nonesterified) fatty acids (FFA or NEFA). The lipoproteins represent a whole spectrum of lipid molecules containing varying proportions of phospholipid, cholesterol (free and esterified), protein (polypeptide), glyceride, and water. The lipoproteins have been classified according to their behavior in the ultracentrifuge, by their migratory behavior during electrophoresis, by their principal N-terminal amino acid residue, by their solubility characteristics, and other ways (155, 194). The density of the lipoprotein molecule is largely a function of the proportion of lipid contained within it; hence, the more "obese" the molecule, the lower its density.

The lipoprotein species with the lowest density are the chylomicrons; the remaining species can be further divided according to their electrophoretic migration with alpha globulins and beta globulins into two groups, the lower density (beta) lipoproteins and the higher density (alpha) lipoproteins.

The free fatty acids are present in a relatively low concentration in plasma under basal conditions (approximately 0.2 to 12.0 meq/liter). However, they appear to have a rapid turnover rate. They travel in the circulation bound to albumin and per-

haps to other substances, and consist principally of fatty acids common in the diet, such as palmitate, stearate, oleate, and linoleate.

Chylomicrons

The elaboration of chylomicrons by the intestinal mucosa has been discussed. These small particles enter the systemic circulation via the intestinal lacteals and thoracic duct. The chylomicrons in the blood are responsible for the visible lipemia that occurs after a meal containing an appreciable quantity of fat. Similar (but not identical) particles manufactured by the liver seem to be responsible for the lactescence that occurs in uncontrolled diabetes, nephrosis, and carbohydrate-induced hyperlipemia. From an analytical standpoint, chylomicrons have been characterized as the material floating at the top of a tube when chyle or serum is layered under saline of density 1.006 and centrifuged for a few minutes at high speed. Varying speeds and time of centrifugation have been suggested, but it is assumed that the lower the speed and the shorter the time of centrifugation, the purer will be the chylomicron fraction (71). One procedure (135) uses 9500 *g* for 10 min. The actual density of chylomicrons is 0.94 *g* per ml.

When chylomicrons are released into the systemic circulation from the thoracic duct, they are removed with considerable rapidity by the liver and extrahepatic tissues. The mechanisms of removal are incompletely understood; however, these small fat particles apparently are not hydrolyzed to any appreciable degree in the circulating blood, although evidence for intravascular hydrolysis has been presented (62). To some extent, fatty acids may be split away from chylomicron triglyceride through the intervention of the enzyme, lipoprotein lipase, but this action probably occurs primarily at endothelial surfaces and other cell membranes and not in the main stream of the circulation (71).

More important mechanisms for chylomicron removal may include direct diffusion into cells through "pores," and phagocytosis by appropriate cells. When the subject is in the postabsorptive state and carbohydrate no longer is readily available, a larger proportion of the chylomicrons from a test meal of fat will be removed by liver and muscle; when excess carbohydrate is available (that is, during hyperglycemia), the chylomicrons are shunted to a greater extent to the fat depots. The clearing of visible lipemia after ingestion of fat may be inhibited if a

previous fat load has been given and has recently been cleared. Although a large amount of chylomicron fatty acid is directly oxidized, some of it may recirculate in the form of free fatty acid. Thus, a variable rise in free fatty acids occurs in blood during the course of an alimentary lipemia (71, 72).

The Lipoproteins

In normal human plasma, the lipoproteins constitute approximately 12 to 15 per cent of the total protein (155). A fundamental difference between the lipoproteins and the remainder of the plasma proteins is that the former are lipid-laden molecules with relatively low density. The plasma lipoproteins exhibit densities from 0.9 to 1.2, in contrast to densities of 1.26 to 1.38 for most other proteins. Thus, the ultracentrifuge has become a useful tool in the separation of the plasma proteins and lipoproteins, utilizing measurement of the differing sedimentation rates of molecules in solvent systems of known density. Gofman and his associates (78, 79, 135) have used a sodium chloride solution with a density of 1.063 to differentiate lipoproteins. These workers have also introduced the " S_f " nomenclature which is used to describe the rates of flotation (varying S_f values) of the various lipoproteins in sodium chloride of density of 1.063. Such rates of flotation are measured in Svedberg units (S_f unit, 10^{-13} cm *g* sec⁻¹ dyne⁻¹). Apparently the S_f value is dependent on the density, shape and size of the lipoprotein molecules (155).

A plethora of terminology relating to the lipoproteins has evolved depending on methods of isolation and identification (71, 78, 134). The subdivisions sometimes have been rather arbitrary, yet certain correlations have been made as, for example, between the ultracentrifugal and electrophoretic behavior of the lipoproteins. It has been demonstrated that there are two major groups of lipoproteins (three if chylomicrons are included) in human plasma: 1) high-density lipoproteins (density > 1.063), or α -lipoprotein by virtue of their electrophoretic mobility; 2) low-density (< 1.063) or β -lipoproteins. The latter (< 1.063) include the classes S_f 0-400 of Gofman (78). The chylomicrons (density 0.94; see above) have virtually no electrophoretic mobility, but exhibit no definite line of demarcation from the S_f 400 low-density lipoproteins, and their S_f value may reach 40,000. Studies of the protein moiety of the lipoproteins have yielded information which may further help characterize the ultracentrifugally separated fractions. Information is available (71)

with respect to molecular weight, end group analyses for specific peptide chains, amount and type of N— and C— terminal amino acids, etc. Such information remains preliminary in nature. A schematic conception of the various human plasma lipoproteins is shown in figure 4.

The lipid moieties of the various lipoproteins (other than chylomicrons) may comprise from 40 to (perhaps) 90 per cent of the molecule. These include a small amount of free fatty acids, and virtually all the esterified fatty acids as esters of glycerol or more complex alcohols, and cholesterol. Free cholesterol also is present. Normal human postabsorptive plasma contains approximately 400 mg per 100 ml esterified fatty acids. Approximately 70 per cent of such fatty acids exist as triglycerides and phospholipids, and the remainder as cholesterol esters (141). Small amounts of esterified fatty acids may be found as diglycerides and monoglycerides, cerebroside and acetals (71).

Despite the high proportion of lipid in the lipoproteins, they have the chemical and physical characteristics of protein molecules. Such behavior suggests that the protein moiety is on the surface of the molecule. For instance, it has been estimated (35) that a chylomicron of $0.5\ \mu$ may be covered completely by protein, assuming the protein to be all at the surface and constituting 1.5 per cent of chylomicron.

micron. However, it has been pointed out that in the larger β -lipoprotein there is only enough protein to cover about half the surface, assuming a thickness of one peptide chain. On the basis of titration data, Oncley *et al.* (154) have postulated a kind of mosaic surface comprising both peptide and phospholipids, the latter being oriented with their charged groups at the surface.

Under ordinary circumstances, the alpha lipoproteins, or high-density lipoproteins, probably do not transport triglyceride for oxidative purposes. Recent studies (176) with labeled amino acids have suggested that the plasma does not contribute a major portion of the protein found in either the chylomicrons or the high-density lipoproteins in thoracic lymph. Since the cells of the intestinal mucosa incorporate amino acids into proteins having the same electrophoretic mobility as chylomicron protein, it was theorized that the intestine may be the source of the protein of both the high-density (alpha) lipoproteins and the chylomicrons.

The alpha lipoproteins contain approximately 40 per cent lipid; are not remarkably influenced by diet or fasting and do not increase with age. In terms of blood level, they are relatively stable.

In contrast, the low-density (beta) lipoproteins, which contain 75 per cent or more lipid, are labile; they are affected by diet, fasting, age and gonadal

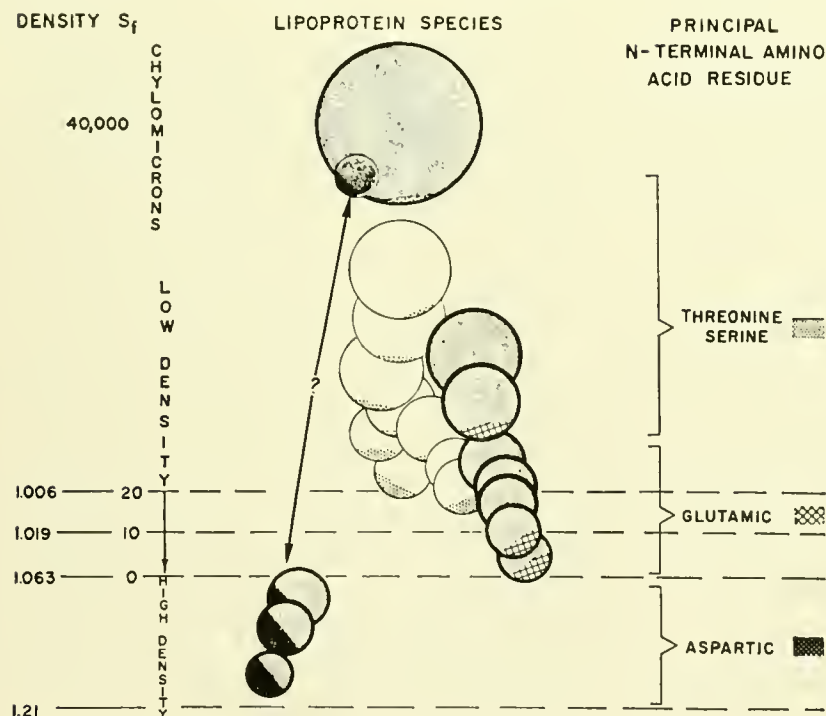


FIG. 4. Schematic conception of human lipoproteins. Cross-hatching or stippling represents polypeptide portions of the molecules. [From Frederickson & Gordon (71).]

hormones, and by a variety of other influences. In fasting states and when carbohydrate utilization is decreased, serum levels of these low-density lipoproteins tend to increase; however, appreciable rises in concentration of such molecules occur only after the fast has been sustained. Ordinarily, such a rise in circulating beta lipoproteins is preceded by an increase in plasma levels of free fatty acids.

There is some evidence that lipoprotein interconversions occur and that, as fatty acids are split off a low-density lipoprotein molecule, its density progressively increases. When heparin is administered, thereby stimulating lipoprotein lipase activity, the interconversion process is greatly accelerated (62).

Free Fatty Acids

The free fatty acids comprise less than 10 per cent of the total fatty acids found in plasma. Strictly speaking, these acids are not "free" since they circulate bound to albumin. Each molecule of albumin can bind two or more molecules of long-chain fatty acid (83).

The free fatty acids represent one important form in which fatty acids are transported from sites of storage (fat depots) to working cells (see above). They do not appear to derive directly from dietary fat. However, dietary fatty acids with chain lengths of C_{10} or less, a very small fraction of fat in the diet, may enter the circulation from the gut via the portal vein in the "free" form (28), although their esterification with glycerol by the intestinal mucosa may also occur (160). Actually, the level of circulating free fatty acids falls after a normal meal. On the other hand, during the course of clearing of alimentary lipemia, a variable fraction of the circulating free fatty acids may originate from chylomicron triglyceride (71).

Studies of the distribution of C^{14} -labeled palmitate (bound to albumin) in rats 15 min after intravenous injection have disclosed a general uptake of the label by various organs and by muscle. Liver lipids were particularly active, whereas adipose tissue had no detectable activity (53). If such experiments can be considered representative of the behavior of free fatty acids under normal circumstances, it would seem that the plasma free fatty acids are removed rapidly in various parts of the body, with subsequent oxidation or esterification, depending upon metabolic circumstances.

There is growing evidence that the free fatty acids constitute an important source of the body's energy in the fasting state; they are released in increasing

amounts by the adipose tissue and used very rapidly at times when carbohydrate utilization is diminished (52). Experimentally induced elevation of the blood sugar or of blood amino acids (94) results in a reciprocal drop in plasma levels of free fatty acids.

Calculations suggest that the circulating free fatty acids probably do not supply more than 50 per cent of the energy in the fasting state; hence, it may be suspected that another important source of energy during fasting is esterified fatty acid (71). Isotope studies have shown that the fatty acid turnover is much more rapid in triglyceride than in cholesteryl ester and phospholipid (13). Thus, the serum glycerides may well function as a major vehicle for transport of esterified fatty acid to sites of utilization.

Ordinarily, in the postabsorptive state, triglyceride moieties travel in the blood as parts of low-density lipoprotein molecules that are neither large nor numerous enough to affect the gross clarity of the serum. However, under conditions of metabolic stress, and in certain disorders, lipoproteins of very low density appear in the circulation in quantities sufficient to render the plasma lactescent. It is unlikely that such particles can be released directly from the fat depots and evidence is accumulating that they originate from the liver.

Role of the Liver

The liver plays a major role in the synthesis and disposal of lipids and lipoproteins. With the exception of the chylomicrons, it appears that lipoprotein manufacture takes place principally, if not exclusively, in the liver. The various factors that influence hepatic synthesis of lipoproteins are not well understood. The process whereby the intestinal mucosa handles dietary fats and transforms them into chylomicrons, some of which are removed by the liver, has been discussed already. Adipose tissue releases fat in the form of free fatty acids "bound" to albumin. These acids also are extracted in appreciable quantities by the liver. Carbohydrate and protein can be converted into fat by the liver. In short, the liver is presented with lipid from several sources, and can itself synthesize lipid, including cholesterol and phospholipid. Thus, the lipoproteins that the liver manufactures and sends out to the circulation are made from a variety of building blocks and are subject to a variety of metabolic influences including diet and hormones. These concepts concerning the origin of serum lipids are shown in schematic form in figure 5. In the case of certain lipids, such as cholesterol, the liver is the

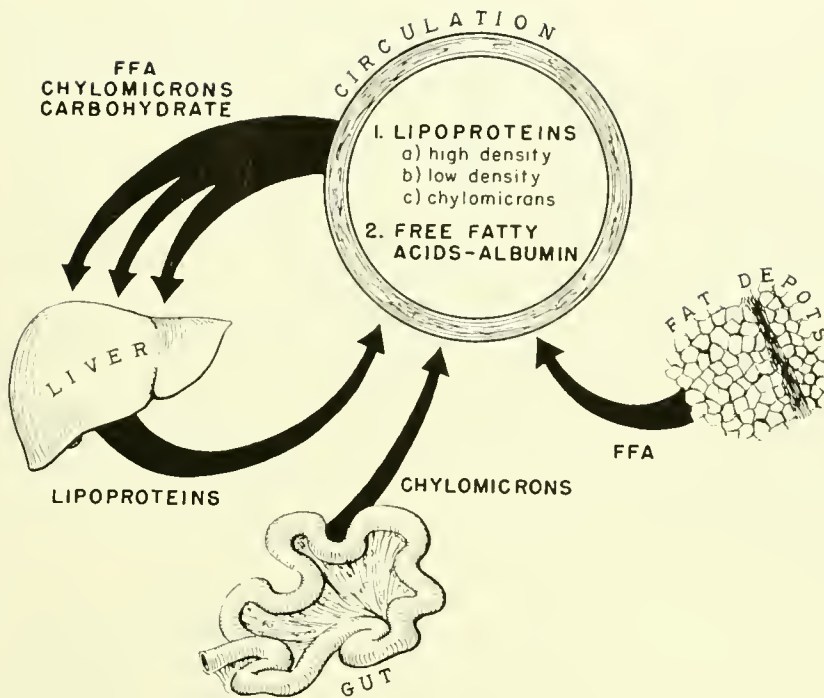


FIG. 5. Origins of serum lipids.
[From Van Itallie & Felch (201).]

major organ of catabolism and excretion. Elaborate mechanisms exist in the liver for disposal of the steroid nucleus of cholesterol, since the body lacks the mechanisms capable of opening the rings of phenanthrene-like structure.

Cholesterol Disposal

As mentioned above, cholesterol represents a special disposal problem. Fatty acids and glycerol are readily metabolized, and phospholipids are freely miscible with water and can be degraded rapidly. On the other hand, although the isopropyl side chain of the cholesterol molecule can be oxidized, with formation of bile acids and certain hormones, the steroid nucleus itself is not degraded.

It is now established that bile acids constitute the major catabolic end products of cholesterol metabolism in man and in a variety of animal species (17, 18, 97). In man, conversion of cholesterol to bile acids occurs in the liver. The biochemical details of this conversion have not been completely worked out. It is generally agreed that in man two "primary" bile acids (hydroxycholanic acids) result from catabolism of cholesterol in the liver: cholic acid and chenodeoxycholic acid (fig. 6). Five important biochemical changes must occur in the cholesterol molecule, and not necessarily in the order listed: *a*) isomerization of the 3 β -OH into 3 α -OH; *b*) saturation of the 5:6

double bond; *c*) hydroxylation at the 7 position (chenodeoxycholic) *d*) hydroxylation at both 7 and 12 positions (cholic); and *e*) oxidation of the terminal isopropyl group resulting in a C-24 acid (cholanic). The resultant bile acids are secreted into the extra-hepatic biliary system as micellar conjugated compounds with either glycine or taurine. In man the conjugation process favors glycine by a factor of three (18). In the intestine the bile acids may undergo further chemical transformations attributed to intestinal microorganisms, giving rise to "secondary" bile acids. For example, cholic acid will lose its 7 α -OH group to yield deoxycholic (3 α , 12 α -hydroxycholanic) acid, and in a similar manner chenodeoxycholic acid will yield lithocholic (3 α -hydroxycholanic) acid. Thus the 7 α -dehydroxylation is a bacterial function. A number of additional bacterial metabolites of hepatic bile acids have been found in human feces, although their importance quantitatively has not been determined (111). In addition, the bacteria split the conjugated compounds into glycine, taurine and their corresponding bile acids. Most of the bile acids are reabsorbed from the intestine into the liver via the portal vein. A small portion is excreted in the stool in unconjugated form. In the normal gastrointestinal tract virtually no cholic acid can be identified in the feces.

It has been estimated that the normal adult individual synthesizes about 1.2 g of cholesterol per day. Approximately 70 per cent of this amount (0.8 g) is

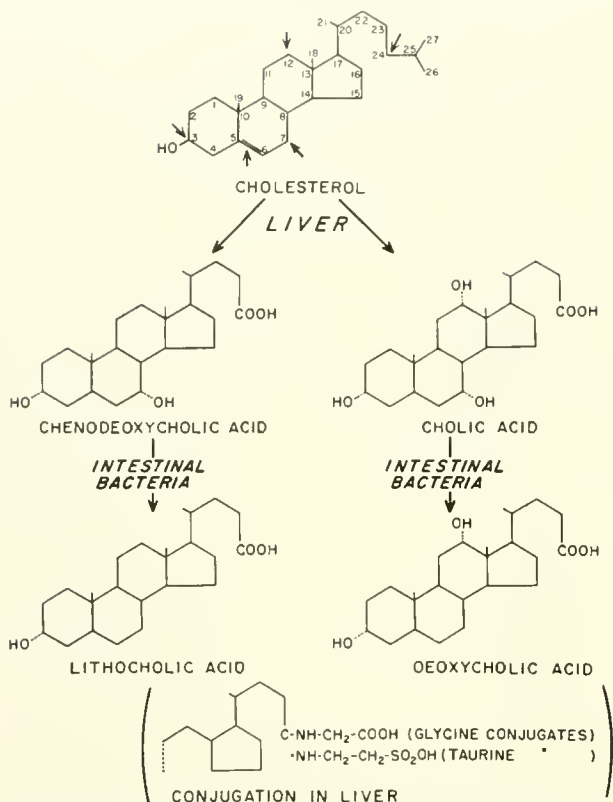


FIG. 6. Formation of "primary" and "secondary" bile acids in man. (From Van Itallie & Hashim, *M. Clin. North America*. In press.)

excreted as bile acids, and a portion of the remainder is excreted in the feces as cholesterol, coprostanol, cholestanol, and other nonacidic sterols. The newly formed bile acids are excreted into the small intestine and participate in an enterohepatic cycle through which 20 to 30 g of bile acids circulate per day (fig. 7). The net loss of bile acids in the feces normally corresponds to the amount converted from cholesterol in the liver.

That bile acids are the major catabolic products of cholesterol has been suspected for about a century. However, this fact was clearly established in 1943 by Bloch *et al.* (26) who demonstrated that, when cholesterol labeled with deuterium was administered to dogs, a minimum of two-thirds of the label appeared in the excreted bile acids. These observations have now been amply confirmed by studies involving use of C¹⁴-labeled cholesterol, notably by Siperstein *et al.* (191, 192), Bergström *et al.* (17, 18), and others.

The behavior of the enterohepatic cycle of bile acids profoundly affects the rate of cholesterol conversion to bile acids. This rate in turn appears to influence plasma cholesterol concentration. Rats with

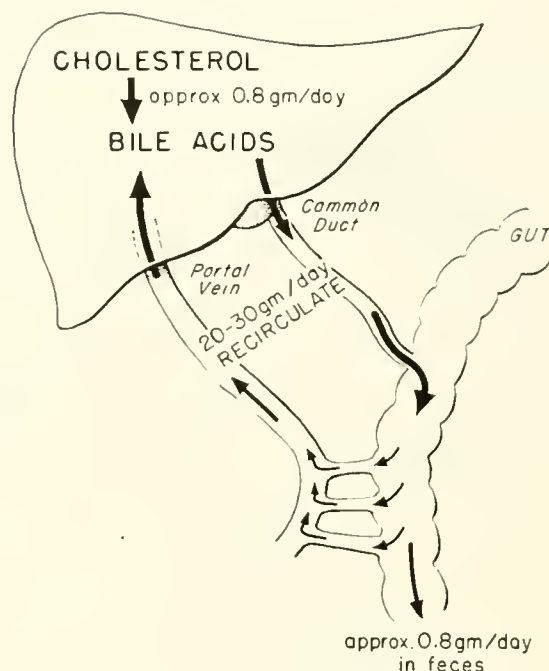


FIG. 7. Enterohepatic cycle of bile acids. [Adapted from Bergström (18).]

indwelling cannulae in the common bile duct exhibit a 10-fold to 15-fold increase in bile acid output through the externalized cannulae compared with the fecal bile acid output of intact rats (18). This also has been observed clinically in patients with common duct intubation. Conversely, in animals with experimental ligation of the common duct (41), and in patients with cholestasis (202), the rate of conversion of cholesterol to bile acids decreases. Moreover, in such situations cholesterol synthesis actually may increase, sometimes with marked elevation of serum cholesterol.

FACTORS THAT INFLUENCE SERUM LIPIDS

Serum lipid levels result from a complex interaction between host and environment (157). Genetic disorders such as familial hypercholesteremia and essential hyperlipemia are associated with gross abnormalities of serum lipids. Among the environmental factors, diet and "stress" have attracted particular attention. Certain diseases also have conditioning effects on serum lipids. Included in this category are nephrosis, hypothyroidism, biliary cirrhosis, diabetes mellitus, pancreatitis, and others. In addition, such factors as age, sex, race, culture, occupation, exercise, body composition, and cigarette smoking have been

regarded by investigators as capable of exerting a significant influence on serum lipids.

It is much simpler to speak of "abnormalities" in serum lipids than to define what is "normal." The difficulty has arisen because of a discrepancy between what is statistically normal and what is probably physiologically desirable. Many authorities now believe that statistical means for serum total cholesterol in a population (like that of the United States) that is beset with cases of atherosclerosis, clinical and subclinical, may be misleading if they are used as criteria of biologic normality. For example, in population groups in which clinically manifest atherosclerosis is very rare, the mean serum total cholesterol is frequently at least 30 per cent lower than it is in the United States (118).

Stress

Despite many attempts to characterize "stress," this phenomenon remains to be defined in generally acceptable terms and its physiologic effects codified. The "epidemiology" of stress is exceedingly complex. The response of the individual to his environment seems to be much more critical than the events overtly taking place in the environment. Hence, it is difficult to assess the degree of stress inherent in a given occupation unless one also knows how the individual is reacting to the "life situation" with which he is confronted. For these and other reasons the effect of stress on serum lipids remains controversial (11, 179). It has been reported that students display a transient elevation of the serum cholesterol level immediately prior to important examinations (197) and that accountants exhibit similar elevations when deluged with income tax returns (73). Even if it is granted that such changes occur, it is not yet known whether the lipid elevations result principally from direct neurohumoral stimulation or because of some associated change in the habits of the person concerned. For example, it is well known that under stress, activity rates may change and certain persons may eat more or otherwise change their pattern of living.

There is some evidence that a certain type of "personality profile" is associated with predisposition to coronary heart disease and that patients with such a profile secrete significantly more epinephrine and norepinephrine than control subjects (74, 75, 147). The coronary-prone individual is characterized as exhibiting excessive, frankly competitive drive and an enhanced sense of time urgency (42). In addition,

this type of individual may display a rapid, frequent, forced, audible inspiration, tense facial and body musculature, frequent fist clenching and a propensity for hastening the pace of conversation. Such individuals have been found to have higher serum cholesterol and increased urinary excretion of vanillyl mandelic acid than those exhibiting the converse of this behavior pattern. Vanillyl mandelic acid (VMA) constitutes about 75 per cent of the metabolic end products of norepinephrine and epinephrine. It has already been mentioned that these catecholamines stimulate mobilization of free fatty acids from adipose tissue. Chronic administration of epinephrine (187) has been found capable of inducing a rise in serum cholesterol and phospholipids. Presumably this effect is secondary to fatty acid mobilization from adipose tissue. It is too early to draw any conclusions from attempts to relate coronary proneness to behavior pattern and catecholamine excretion rate.

Sex

Surveys have shown that American females between 20 and 50 years of age have significantly lower levels of serum total cholesterol and low-density lipoproteins than age-matched American males (129). It is obvious that the mode of life of females usually differs from that of males in a given culture, and the effect of such a differing pattern of activity upon serum lipids and susceptibility to coronary heart disease is difficult to assess. Nevertheless, a number of studies have suggested that the endocrine differences between male and female can adequately account for the fact that during their reproductive period, women have lower levels of certain serum lipids. In general, administration of androgenic hormones to patients is associated with a rise in concentration of β -lipoproteins, while estrogenic hormones induce a fall in this same lipoprotein fraction (58, 59).

Whether such differences in lipid levels can account for the established disparity in susceptibility to coronary-artery disease between men and women remains to be proved. However, supporting evidence is to be found in the fact that women who have undergone oöphorectomy have "male" serum lipids and an increased incidence of coronary-artery disease (212), and that men treated with estrogen for prostatic carcinoma have "female" lipids and less than the expected degree of atherosclerosis (173). A recent report from Edinburgh (151) has revealed that, over a five-year period, one hundred men who had recovered from a myocardial infarction, and who were

treated with estrogen daily, showed appreciable lowering of their serum cholesterol levels without a significant effect on their death rate, compared with a comparable untreated control group. The apparent lack of protection may have been related to the choice of subjects who already had experienced myocardial infarction.

Dietary Fatty Acids

It is now established that diet can have a profound influence on serum lipids; indeed, the relation of diet to serum lipids has been under intensive study in recent years. More information is available concerning the influence of dietary fat on serum lipids than about the effect on serum lipids of other dietary constituents. Not long ago, it was believed that the total quantity of fat in the diet was the major factor affecting serum lipids (117). In particular, the American diet providing 40 to 45 per cent of its calories as fat was implicated as being responsible for the relatively high serum cholesterol values observed in adults in the United States. It is now clear that the "quality" of the fat in the diet is of primary importance in determining the response of the serum cholesterol fraction, although the relative proportions of carbohydrate and fat in the diet appear to influence the serum triglyceride concentration. It is of interest to review briefly some of the events that have led to these conclusions.

In 1933 Schoenheimer (183) reported that feeding a wholly vegetarian diet to a patient with hypercholesteremia resulted in marked lowering of serum cholesterol. During the ensuing two decades, relatively little further information of this kind was gathered. Extensive studies regarding the metabolism of cholesterol and other lipids were undertaken during this time and significant discoveries were made. It was found that cholesterol is readily synthesized in the body from small carbon fragments (171), and that the major catabolic pathway for cholesterol involves conversion to bile acids (26).

In 1952, Groen and associates (87) demonstrated by means of well-controlled and prolonged experiments that substitution of vegetable for animal fats in the diet can lower serum cholesterol in man, even if the total fat content remains unchanged. During the same year Kinsell and associates (122) reported that ingestion of diets containing relatively large amounts of vegetable fat consistently resulted in a significant fall in the level of serum cholesterol and

phospholipids in human subjects. These observations have been amply confirmed (2, 3, 22, 36, 123, 140).

It soon became apparent that the fatty acid composition of dietary fat was of primary importance in determining serum cholesterol response. The experiments in which vegetable oils were used stimulated interest in the possible role of the essential fatty acids. Subsequently, Kinsell and associates (124) concluded that the major cholesterol-lowering ingredient in various vegetable fats was, in fact, linoleic acid. Then, in a series of well-controlled comparative experiments in man, utilizing formula diets deriving 40 per cent of their calories from fat, Ahrens *et al.* (4) observed that the effects on serum cholesterol of various edible fats could be related to their iodine value. Thus, fats with high iodine values such as safflower, corn, and cottonseed oils proved to be relatively hypocholesteremic, while fats with low iodine values such as palm oil, beef, butter, cocoa butter, and coconut oil tended to raise the serum cholesterol level. Intermediate or neutral effects on serum cholesterol were obtained with fats with intermediate iodine values such as peanut and olive oils. In a later study (5) the Rockefeller group found that menhaden oil, a fat virtually free of linoleic acid and yet with an extremely high iodine value (1, number 180) was at least as effective as corn oil in lowering serum cholesterol. Keys and associates (120) have proposed a formula designed to predict the effect of a given pattern of dietary fatty acids on serum cholesterol in man. The formula attempts to take into account the different roles of the saturated, monounsaturated, and polyunsaturated fatty acids in the diet; however, it remains to be demonstrated that such an analysis can be applied successfully in a variety of dietary situations (4).

In any event, it is clear that serum levels of cholesterol and low-density lipoproteins can be changed significantly when the pattern of fatty acids in the diet is rearranged. When the glycerides of a dietary fat contain predominantly saturated long-chain fatty acids, concentrations of serum total cholesterol and certain low-density lipoproteins tend to rise. When such dietary glycerides contain an appreciable proportion of polyunsaturated fatty acids (whether essential or not), serum cholesterol, and low-density lipoproteins tend to decrease. The degree of change in serum lipids seems to depend upon the magnitude of change in the pattern of the fatty acids in the diet. Thus, it may be necessary to double or triple the polyunsaturated fatty acid content of the diet (without change in the total fat intake) to induce an appreciable lowering of serum cholesterol. However, even

when such drastic changes are made in the diet, variations in individual responses are great (113).

Essential Fatty Acid (EFA) "Deficiency"

The fact that serum lipids can be lowered, when dietary fats rich in polyunsaturated fatty acids are fed, has stimulated considerable interest in the biochemistry of the essential fatty acids (linoleate, arachidonate, etc.), their role in nutrition, and, in particular, their possible role in the metabolism of cholesterol. Excellent reviews and discussions of these subjects are available (1, 51, 106, 146, 189). Holman (106) has suggested that the term essential fatty acid (EFA) include "only those substances which are active both for growth and for maintenance of dermal integrity, limiting the term to linoleic and arachidonic acids and to such other acids as may be derived metabolically from them." As has been pointed out by Aaes-Jorgensen (1), this definition leaves out linolenic acid and C₂₂ polyenoic acids from brain phosphatides which have been shown by Thomasson (50, 198) to be active only as growth factors.

Despite numerous studies since 1929, when Burr & Burr (40) first recognized EFA deficiency in young rats, the EFA requirement for human adults has not been determined. In fact, EFA deficiency in adult man has not been demonstrated. In 1958, the Food and Nutrition Board of the National Research Council (65) suggested that one per cent of calories should be the minimum daily EFA allowance for humans. In any reasonable variation of the American diet, this quantity is certainly present. In the human infant, however, Hansen and associates (90) have shown that linoleic acid is definitely required in amounts as little as 1.3 per cent of daily dietary calories to prevent or cure certain dermatoses. Infants fed low fat diets (EFA-deficient) exhibited low serum values for dienoic and tetraenoic fatty acids, and high serum values for trienoic acids. The reverse serum picture was obtained following addition of linoleic acid to the diet.

On the basis of evidence now available it seems unlikely that Sinclair's (190) hypothesis attributing "nutritional" hypercholesteremia and atherosclerosis to essential fatty acid deficiency is correct. Patients with clinically manifest atherosclerosis and elevated levels of serum total cholesterol do not necessarily exhibit a lack of linoleic acid in their serum or depots (103, 112). Moreover, Ahrens and associates (5) have shown that formula diets, containing as their source of fatty acids the nonessential polyethenoid fatty

acids predominating in certain fish oils, lower serum cholesterol as effectively as formula diets containing oils exceedingly rich in linoleic acid.

Chain Length, Unsaturation, and Melting Point

Serum lipid responses to dietary fats have been correlated with certain characteristics other than essential fatty acid content or iodine value. Two major variables affecting the physical and biochemical properties of fatty acids are degree of unsaturation and chain length (table 1). For example, linoleic acid (2 double bonds) and stearic acid (no double bonds) have the same chain length, and yet the melting point of linoleic acid is -11 C, whereas that of stearic acid is 69.4 C. Stearic acid (C₁₈) and capric acid (C₁₀) are both fully saturated acids; however, the melting point of the shorter chained capric acid is 31.5 C.

Since the melting point of a fat (as well as other characteristics) depends upon the component fatty acids, it is possible to lower the melting point of a triglyceride either by increasing the unsaturation or by reducing the chain length of its fatty acids. Accordingly, many of the physical characteristics of a fully saturated fat containing shorter chain saturated fatty acids may resemble those of a highly unsaturated fat containing predominantly long-chain monounsaturated or polyunsaturated fatty acids.

As previously mentioned, when subjects are fed diets containing as their fat source solid fats such as butter and mutton tallow, their cholesterol levels tend

TABLE 1. *Classification of Fatty Acids According to Chain Length and Degree of Unsaturation*

| Category & Typical Acid | Number of Carbon Atoms* (Always even numbered) | Number of Double Bonds | Typical Food Sources |
|--------------------------------------------------|---------------------------------------------------|------------------------|-----------------------------------------|
| 1. Medium Chain Saturated (Lauric) | 6 - 12 (12) | None | Milk fat Coconut oil |
| 2. Long Chain Saturated (Palmitic) | 14 - 24 (16) | None | Practically all animal & vegetable fats |
| 3. Long Chain Monounsaturated (Oleic) | 14 - 22 (18) | One | Most fats and oils |
| 4. Polyunsaturated, Essential (Linoleic) | 18 - 20 (18) | Two-Four (Two) | Seed fats (Organ fats) |
| 5. Polyunsaturated, Non-essential (Clupanodonic) | 18 - 26 (22) | Three-Six (Five) | Fish oils |

to remain elevated or to rise. When highly unsaturated liquid fats such as corn oil and menhaden oil are substituted isocalorically for the "hard" fats in the diet, serum cholesterol levels usually fall appreciably. A reasonable correlation can be made between the physical state of a fat and its effect on serum cholesterol. It has been suggested that the cholesterol-lowering effect of the liquid oils may be a function of the constituent polyunsaturated fatty acids and that these fatty acids have an effect by virtue of their polyethenoid configuration.

Recently, it was reported that a synthetic medium-chain triglyceride, a liquid with a melting point below 0°C, made up entirely of saturated fatty acids of chain lengths ranging from C₆ to C₁₂, can lower serum cholesterol significantly when substituted for butter in a formula diet (96). Such results are of interest since medium-chain triglyceride (MCT) is devoid of polyethenoid fatty acids and has an iodine value of less than 1.0 (that of butter is approximately 40). Although the preparation is highly saturated, its shorter chain fatty acids confer upon it many of the physical characteristics of the natural vegetable oils rich in long-chain polyunsaturated fatty acids.

Since medium-chain fatty acids may be metabolized differently from longer chain fatty acids, the results with medium-chain triglyceride may not help one interpret the cholesterol-lowering effects of the highly unsaturated oils. On the other hand, such studies have again called attention to the possible importance of the physical properties of fatty acids apart from the number and location of their double bonds.

There remains a great need for further characterization of dietary glycerides in order that their physicochemical characteristics may be better related to their effects on serum lipids. The mechanisms whereby dietary fats influence cholesterol metabolism still are not well understood. The picture is further complicated by the complex nature of the dietary glycerides. As pointed out earlier, 64 different fatty acids have been identified in butter. For a time it was believed by some investigators that the hypercholesteremic effect of butter was due to its relatively high content of shorter chain saturated fatty acids. Studies employing synthetic glycerides of simplified fatty acid composition were helpful in clarifying this problem inasmuch as it was possible to study the effect on serum lipids (96) of a synthetic medium-chain triglyceride (MCT) containing predominantly the very fatty acids thought to be hypercholesteremic. As a result of such experiments it was shown that in rela-

tion to butter the MCT preparation was actually hypocholesteremic.

Dietary Cholesterol

Since the early work of Ignatowski (110) and Anitschkow (10) on experimental atherosclerosis in rabbits, dietary cholesterol has been an essential ingredient of diets used to induce hypercholesteremia and atherosclerosis in a variety of animal species. Not long ago, it was fashionable to prescribe diets low in cholesterol for patients with an elevated serum cholesterol. As cholesterol metabolism in man was studied more intensively, it became evident that the liver normally synthesizes about three times as much cholesterol per day as is consumed in the average diet. It was further learned that an increased intake of cholesterol is likely to result in a proportionate inhibition of cholesterol manufacture. Subsequently, carefully controlled studies by Keys *et al.* (119) and others have suggested that, within wide limits, variations in the cholesterol content of an ordinary diet do not affect serum cholesterol levels to any significant degree, provided other elements in the diet are constant. Such results have encouraged many physicians to abandon use of diets specifically low in cholesterol in treating patients with hypercholesteremia.

Despite such negative reports, the influence of dietary cholesterol on serum cholesterol in man continues to be a subject of investigation and controversy. Beveridge *et al.* (23) have recently reported that the addition of relatively small amounts of cholesterol to formula diets can raise serum cholesterol levels, depending on the nature of the accompanying fat. Indeed, these investigators attribute the hypercholesteremic effect of butter in part to its content of cholesterol. Keys (121) has reviewed the results of Beveridge and associates and has questioned their significance. Connor *et al.* (45) have studied the effect of adding or subtracting moderate amounts of cholesterol as egg yolk in diets equivalent in amounts and composition of fat. In their studies, the addition of 475 to 1425 mg cholesterol (the amount present in one to three large eggs) raised serum total cholesterol by an average of 68 mg per 100 ml. On the other hand, crystalline cholesterol added to the diet in amounts ranging from 1200 to 3600 mg per day increased the mean cholesterol level by only 18 mg per 100 ml.

It would seem that the effect of crystalline cholesterol added to the diet cannot be equated with the effect of the cholesterol that occurs naturally in food.

It is possible that the differences in response to these two forms of cholesterol relate to considerations of solubility of this sterol in dietary fat. Recently, it has been pointed out (37) that cholesterol is more soluble in the saturated than in the polyunsaturated fats.

Practicable Diets

It is of considerable practical interest that palatable diets can now be devised that are rich in polyunsaturated fatty acid content and provide the same proportion of fat to which Americans are accustomed. At present, need exists for controlled studies in man to determine the effects on serum lipids of "normal" diets exhibiting a variety of fatty acid patterns. Attempts in this direction have begun (46, 93, 111). Earlier experiments with semipurified formula-type regimens suggested that when the ratio of polyunsaturated to saturated fatty acids (P:S ratio) in the diet was increased, serum cholesterol usually could be lowered.

Approximately 5 years ago, experiments were begun to determine whether everyday diets could be altered so as to reduce serum cholesterol levels and yet remain palatable and acceptable to most individuals. From progress reports of these studies, it is now clear that manipulation of the fatty acid pattern of the diet is effective in lowering serum cholesterol in most subjects with cholesterol levels higher than 230 mg per 100 ml. The change in pattern is effected principally by substituting one form of dietary fat for another in order to increase the P:S ratio. In practice, this change involves a drastically decreased consumption of butter fat and of certain margarines, and a reduced intake of meats from ruminants, such as bovine animals and sheep. At the same time, consumption of poultry, fish, nuts, and plant seed oils is materially increased. A typical diet designed to lower cholesterol prescribes an increase in intake of polyunsaturated fatty acids from approximately 15 to 42 per cent of total fat and a decrease in intake of saturated fatty acids from approximately 42 to 15 per cent. The intake of the monounsaturated fatty acid, oleic acid, remains unchanged. Total dietary fat is reduced from 44 to 36 per cent of calories, although this is not an essential feature of the diet.

Such diets are acceptable and palatable. The effect of a diet of similar fatty acid composition on serum cholesterol in 97 men of normal weight, 50 to 59 years old, was determined by Jolliffe *et al.* (113). This study demonstrated the fall in cholesterol by tertiles over a period of 6 months. The upper third, with

cholesterol levels of 270 mg per 100 ml and over, dropped an average of 45 mg per 100 ml. The lower third, with cholesterol values under 230 mg displayed a decrease averaging 16 mg per 100 ml. Similar studies performed on smaller groups of subjects have yielded generally similar results (200).

The fact that it is indeed feasible to lower serum cholesterol levels by dietary means has had and is continuing to have a tremendous impact on the public, the medical and dietetic professions, and the food industry. The public is being made increasingly aware of the possibly ominous significance of an elevated serum cholesterol level in terms of danger from obstructive coronary artery disease. At the same time, there appears to be decreasing use, per capita, of butter and hydrogenated products, and increasing use of liquid vegetable oils, such as corn, safflower, and cottonseed oils.

A number of cookbooks on the subject of fatty acid "control" are now appearing, and the demand for them is great. Recently, several food companies have come out with new margarines with an increased content of *cis-cis* linoleic acid. There is increasing interest in the development of cheeses and spreads and commercial products resembling ice cream, all containing appreciable quantities of linoleate. "Reasonable substitution of polyunsaturated for saturated fats, under medical supervision" has been recommended by an ad hoc committee of the American Heart Association (8). Whether or not diets of this kind will have a clinically useful effect is one of the most urgent questions facing medicine today.

Mechanism of Cholesterol Lowering

The exact mechanism whereby a diet rich in polyunsaturated fatty acids lowers serum total cholesterol (and low-density lipoproteins) remains unknown. A few studies have indicated that when such a diet is fed more cholesterol and its end products (including bile acids) are excreted in the feces. When a diet rich in saturated fatty acids is fed, less sterols and bile acids are excreted in the feces and the serum cholesterol level rises (85, 99, 111).

There appears to be no evidence for direct interference by the polyunsaturated fatty acids with cholesterol synthesis in the liver. However, the ability of the liver to excrete cholesterol and to convert cholesterol to bile acids may depend in part on certain physicochemical characteristics of cholesterol esters or of the lipoprotein molecules of which cholesterol and its esters can constitute a significant portion.

Cholesterol esterifies readily with polyunsaturated fatty acids such as linoleic acid (115). When the dietary fatty acids are predominantly saturated, esters such as cholesteryl oleate and palmitate are likely to occur in increasing amounts and, conceivably, may be less available for excretion and conversion to bile acids by the liver.

Additional Influences on Serum Lipids

Other dietary manipulations also can influence serum lipids (63, 153, 166). A drastic decrease in dietary intake of protein is associated with lowering of serum total cholesterol (and β -lipoproteins) in man (76, 152). High protein intakes above 10 per cent of total daily calories have been found to be effective in lowering serum cholesterol and β -lipoproteins in animals but not in man (153). A substantial decrease in the proportion of fat in the diet may be associated with a lowering of serum cholesterol, but in certain individuals a considerable rise in serum triglycerides may occur (4, 6). Such diets usually contain a large quantity of carbohydrate, much of which gets converted by the body into fat.

There is evidence from studies in laboratory animals and human subjects that the type of carbohydrate in the diet can affect serum lipids. Compared to sucrose, starch promotes bile acid excretion and tends to lower serum cholesterol in the rat (165). It has also been reported that when the carbohydrates of legumes are substituted isocalorically for sucrose in the diets of human subjects, cholesterol levels are reduced to a slight degree (9).

The effect of a given diet on caloric balance must also be taken into account. Patients in negative caloric balance can often have a transient decrease in serum lipids on this basis; on the other hand, during active weight gain, serum lipids tend to rise (142, 204). Weight reduction may induce a decline in serum lipids in persons with hyperlipidemia. It is not certain whether such a decrease occurs only while weight actually is being lost or whether, in some instances, the improvement in serum lipids will be sustained for as long as weight is maintained at a reduced level. However, as was mentioned earlier, during a sustained fast the serum levels of the low-density lipoproteins tend to increase; this contrasts with the decline in serum lipids shown by nonfasting patients in negative caloric balance.

Pharmacologic approaches to lowering serum cholesterol have included use of agents with the following mechanisms of action:

1) Inhibition of cholesterol biosynthesis. Under

this category are included triparanol (138, 193), benzmalecene (15), and possibly nicotinic acid (7, 82, 158). Agents which inhibit cholesterol biosynthesis also may interfere with other important synthetic processes such as steroid biogenesis; hence, they are potentially toxic for man.

2) Inhibition of cholesterol absorption from the gastrointestinal tract. Plant sterols such as sitosterol have been used for this purpose in man (20, 188). The mechanism for inhibition of cholesterol absorption remains to be demonstrated. Moreover, the effectiveness of sitosterol in lowering serum cholesterol in man has been questioned. Studies by Levere and his associates (131) suggested that no decrease in serum cholesterol could be attributed confidently to sitosterol administration, and that any apparent decrease might be caused by great fluctuations in serum cholesterol observed in such studies in man.

3) Promotion of cholesterol degradation. Reference already has been made to the polyunsaturated fatty acids and the possibility that they might act by promoting the rate of cholesterol breakdown to bile acids. Simple addition to the diet of relatively small quantities of polyunsaturated fatty acids cannot be relied upon to induce significant lowering of the serum cholesterol level (159). Pharmaceutical preparations containing linoleic acid and sometimes supplemented with small quantities of pyridoxine and tocopherol offer no advantage over the various linoleate-rich oils such as corn and cottonseed that can be purchased inexpensively at the grocery. Moreover, as mentioned earlier, the polyunsaturated fatty acids, in order to be effective in lowering serum cholesterol, must be consumed in relatively large amounts and their intake integrated with an over-all reduction in the consumption of saturated fatty acids as part of a carefully adhered-to regimen.

An interesting group of substances has been found capable of lowering serum cholesterol by binding bile acids in the gut and thereby promoting their fecal excretion. These are the anion exchange resins (14, 196, 202) that form nonabsorbable complexes with bile acids. Appropriately, they have been termed "bile acid sequestrants" and of these cholestyramine has been studied extensively in man. Cholestyramine is apparently innocuous since it does not seem to enter the body. Long-term effects of bile acid sequestration in man are at present unknown. The net effect of the bile acid sequestrants appears to be similar to that of the polyunsaturated fatty acids; namely, promotion of cholesterol degradation.

Thyroid hormones and their analogues (33, 77, 151) may lower cholesterol by virtue of an effect on bile

acid metabolism (100); however, the exact mechanism remains to be clarified. Studies of *d*-thyroxine in man revealed no reliable dose-response of serum cholesterol over a 6-month period, nor was there a dose which would be effective in lowering serum cholesterol without provoking angina (151).

Neomycin has been reported to lower serum cholesterol and simultaneously to increase fecal excretion of bile acids (81, 82, 181). The influence of neomycin on bile acid metabolism may be related to its profound effect on intestinal flora and the possible damage it inflicts on the villi of the intestinal mucosa.

4) Increased tissue removal of cholesterol. It is suspected that the estrogenic hormones and their congeners (12, 34) may lower serum cholesterol by increasing the activity of the reticuloendothelial system and thereby accelerating the removal of cholesterol-rich lipoproteins from the plasma. Whether cholesterol catabolism is further enhanced within the reticuloendothelial system remains unknown. The effect of estrogens on cholesterol biosynthesis also is not clear; however, there is evidence that estrogen administration is not associated with an increased rate of bile acid excretion. A variety of

other substances (63, 166) too numerous to discuss in detail also are capable of inducing a reduction in serum cholesterol. The four mechanisms for lowering cholesterol that have been described are summarized in figure 8.

BLOOD LIPIDS AND ATHEROSCLEROSIS

Virtually no information based on direct observation is available concerning the relationship in man between circulating lipids and atherosclerosis. The difficulty has been that the tools for diagnosing occult atherosclerosis are inadequate. There is indirect evidence—epidemiologic, experimental, clinical, and pathologic—that sustained elevation of the plasma low-density lipoproteins is associated with an increased rate of atheroma formation. It is suspected that plasma lipoprotein may be “filtered” through intimal cells under arterial pressure and that accumulation of lipid in the subintimal area is accelerated by continued traffic of plasma rich in “unstable” lipoprotein through the arterial wall (153, 201).

Animal experiments have shown that when an increased plasma concentration of β -lipoproteins is achieved by dietary or other means, atherosclerosis usually results (64, 143, 211). The early vascular changes observed in experimental atherosclerosis are believed by many observers to have a close resemblance to early human lesions.

Evidence is also available from studies in man that prolonged elevation of the serum cholesterol is associated with an increased susceptibility to atherosclerosis and its clinical manifestations. In diseases such as diabetes and hypothyroidism in which serum lipids tend to be elevated, the incidence of atherosclerosis also is increased. Moreover, patients with angina pectoris or a history of myocardial infarction tend to have serum lipid levels higher than those of apparently healthy control subjects. This difference in lipid levels is most striking when groups below the age of 45 are compared (201).

Epidemiologic studies of populations in various parts of the world (18) involving correlation of serum cholesterol levels with prevalence of clinically manifest atherosclerosis and presence of the disease at autopsy have given additional support to the proposed relationship between hypercholesteremia and atherosclerosis. Most epidemiologic studies attempting to relate coronary heart disease to levels of serum cholesterol are retrospective in that the subjects studied have already exhibited clinical manifestations of atherosclerotic heart disease. The Framing-

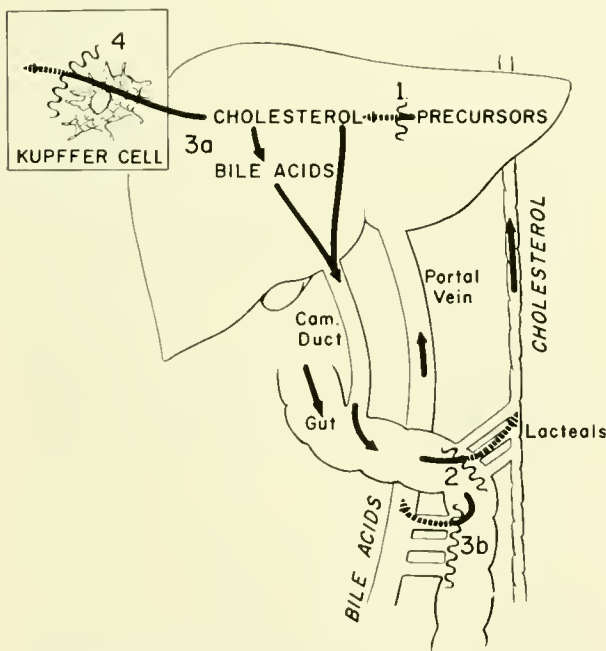


FIG. 8. Mechanisms for lowering plasma cholesterol. 1: Inhibition of cholesterol biosynthesis (triparanol). 2: Inhibition of cholesterol absorption (sitosterols). 3: Promotion of cholesterol degradation—*a*, polyunsaturated fatty acids; *b*, bile acid sequestrants. 4: Increased tissue removal of cholesterol (estrogens). (From Bergen & Van Itallie, *Ann. Internal Med.* In press.)

ham Heart Program (47, 114) is of interest because it has used the prospective approach. In this study, approximately 5,000 individuals originally free of manifestations of overt coronary heart disease in the town of Framingham, Massachusetts, have been followed for 8 years, and the study continues. From the Framingham data, it has been shown that an association exists between a number of factors, other than age and sex, and an increased risk of developing coronary heart disease: these are obesity, hypertension, electrocardiographic evidence of left ventricular hypertrophy, heavy smoking, and hypercholesteremia. Increasing levels of serum cholesterol were found to be associated with increasing risk of developing coronary heart disease. Among the various lipid measurements (excluding cholesterol esters and triglycerides about which data were lacking) serum total cholesterol was found to be the best measurement for predicting the occurrence of overt coronary heart disease. While the results of the Framingham study have been interesting and provocative, the relatively small number of subjects studied make it difficult to arrive at firm conclusions about the relationship between such variables as the serum cholesterol and incidence of obstructive coronary disease. Until larger samples can be obtained there is always a risk of drawing too many unqualified conclusions from insufficient data (132).

In addition to the increased risk of heart disease associated with hypercholesteremia, the increased incidence of coronary atherosclerosis in patients with essential hyperlipemia (hypertriglyceridemia) (139) should be mentioned, as well as the reports that patients with coronary heart disease tend to display elevated levels of serum triglycerides (6) and impairment of rate of clearing of alimentary lipemia (186). Such preliminary observations suggest that the lower-density lipoproteins carrying an increased burden of triglyceride may play a more important etiologic role in coronary atherosclerosis than has been hitherto appreciated.

Although it is common practice to use the term "atherosclerosis" as though it described one disease, evidence has been accumulating that in certain countries where clinically manifest coronary-artery disease is rare, atherosclerosis of the aorta may be quite common (86). Similarly, American women possess a relative immunity to coronary heart disease during their reproductive years; yet they are not equally immune from atherosclerosis at other anatomic sites (174). It is worthy of comment that although coronary heart disease is very common in

patients with familial hypercholesteremic xanthomatosis (primary hypercholesteremia), this disease does not seem to predispose to the development of peripheral or cerebrovascular disease (89). Conversely, coronary heart disease is rare among the South African Bantu, a group in whom serum cholesterol levels tend to be very low; yet, cerebral catastrophes occur as frequently among Bantu as among populations with substantially higher levels of cholesterol (128, 205). Thus, coronary heart disease may prove to be a special manifestation of atherosclerosis, with its own epidemiology and, perhaps, its own biochemical pathology.

Chemical studies of the atheroma have supported the belief that a number of the fatty constituents of the atheroma are derived from the plasma. Studies have demonstrated that the distribution of lipids in early atheroma is roughly similar to that in plasma (104). As the atheromas of human aortas progress in severity, they exhibit a parallel increase in content of carotenoid and cholesterol (25). Since carotenoid is derived entirely from the diet, such observations also suggest that atheromatous lipid derives from the circulation and does not originate *de novo* within the arterial wall. A similar interpretation can be made of the demonstration that linoleic acid, a substance which the body apparently cannot synthesize, is a significant constituent of atheromas (187).

With the advent of gas-liquid chromatography and other improved techniques for lipid separation and identification, it has become possible to obtain more precise information about the lipid constituents of atheromas at various sites and at various stages of evolution (30, 31, 54, 133, 136, 199, 208). It has been reported that the saturated and monounsaturated fatty acid moieties of cholesterol esters tend to accumulate preferentially in early atheromatous lesions. However, linoleic acid also can be found in atheromas in appreciable quantities. A report from Leiden (32) has described the results of detailed analyses of the lipids in aortas and coronary and cerebral arteries in various stages of atherosclerosis. It was found that as the aortic lesions became more advanced their relative content of cholesterol and cholesterol esters increased strikingly. A comparison of the fatty acid composition of "early" and "late" atheromas with uninvolved aorta showed an increase in the proportion of the polyunsaturated fatty acids of cholesterol esters in the older lesions. The phospholipids exhibited a slight increase in their proportion of long-chain saturated fatty acids. Generally similar results were obtained for the circle of Willis, in which the content

of cholesterol esters increased in more advanced lesions while phospholipid content decreased. In the coronary vessels, the content of triglycerides in relatively healthy specimens was quite high; cholesterol and its esters increased with advancing atherosclerosis while glyceride content fell. With respect to fatty acid patterns, the trends with increasing atherosclerosis in coronary and cerebral samples were similar to that shown by the aorta.

The studies reported to date on the lipid composition of atheromas appear to support the impression that the cholesterol esters in the intima and media start by being extremely saturated in comparison with those circulating in the plasma; with increasing atherosclerosis of the wall the apparently healthy parts contain more polyunsaturated cholesterol esters than the adjacent lesions. The mechanism whereby even apparently normal vascular tissue becomes infiltrated by plasma lipids remains unknown. In any event, it seems clear that the fatty acids of the arterial wall, like those of the plasma, are responsive to dietary influences. Hence, this variable (among others) must be taken into account when data reported by various investigators are being compared and evaluated.

It should not be forgotten that a number of environmental and host factors may play a role in the pathogenesis of atherosclerosis. Groen (88) has listed eight exogenous and six endogenous elements that have been given major attention by various investigators. Included in this list are such items as constitution, age, obesity, physical exercise, social class, emotional influence and such concomitant diseases as hypertension and diabetes. This very multiplicity of considerations makes human atherosclerosis an exceedingly complex problem. However, a common pathway still must be defined through which a given influence can operate. In the present discussion the early atheroma has been viewed as a phenomenon secondary to an abnormality of the serum lipids; thus, the lesion can be said to be biochemical first and histologic second.

ROLE OF BLOOD CLOTTING AND THROMBOSIS

Commonly, the dramatic clinical manifestations of atherosclerosis such as myocardial infarction and "stroke" result from acute thrombotic obstruction of an artery. It is generally believed that the atherosclerotic lesion acts as a nidus for thrombus formation which, in turn, occludes the vessel. This assumption is not invariably correct. Arterial thrombosis can

occur at sites where atherosclerosis is minimal or absent, and arterial occlusion by an atherosclerotic lesion can occur without thrombosis. The events that lead to thrombosis *in vivo* still are not clearly understood.

Certain inconsistencies appear if arterial thrombosis is regarded as a simple epiphenomenon of atherosclerosis. Epidemiologic studies have suggested an increase in mortality rates from coronary artery disease in the Western World during the past 25 years without a corresponding increase in atherosclerosis (149). The discrepancy in certain countries between clinical coronary artery disease (rare) and atherosclerosis of the aorta (common) already has been mentioned. In certain experimental animals, in which atherosclerosis has been produced readily by dietary means, production of myocardial infarction has been difficult [although achieved in rats fed high fat diets supplemented with cholesterol, cholic acid, and thiouracil (91)]. Thus, any attempt to relate development of occlusive arterial disease to dietary fat consumption must take into account the role of thrombosis (150). In this regard, Duguid (56) has reviewed and modified a concept introduced by Rokitsansky a century ago relating atherogenesis to fibrin deposition on arterial intimal surfaces. Duguid has shown that arterial narrowing can be produced by organization of mural thrombi with subsequent endothelialization and lipid deposition. The end result is difficult if not impossible to distinguish from "atherosclerosis." Subintimal hemorrhage and other "mechanical" factors have been considered as initiating the process (57). From such a standpoint, lipid deposition in atherosclerosis is thought to be secondary to thrombus formation. However, most of the available evidence still favors the view that lipid deposition in the arterial wall is the primary event in atherogenesis.

The possible influence of dietary fat on blood coagulation has been the subject of several reviews (92, 163). It is clear that the factors involved in maintenance of blood fluidity are complex and deserving of further investigation. Methods for detecting incipient thrombosis in the intact organism are inadequate. A distinction must be made between results obtained by feeding fat on the various coagulation tests *in vitro* and the influence of lipemia on coagulation *in vivo*. There appears to be agreement concerning the accelerating effect of certain dietary and synthetic phospholipids, platelet lipid extracts, and postprandial plasma on the *Stypven* time, a shortening of the clotting time of plasma in the presence of Russell's viper venom. The relevance of these

findings to in vivo coagulation remains unknown. Recently Poole (164) has emphasized the difference between clotting and thrombosis and has pointed out that factors important in clotting may be unimportant in thrombosis. Under the electron microscope, clots and thrombi are different in structure. The thrombus contains areas of closely packed platelets while the clot contains predominantly red cells and a few platelets distributed at random in a fibrin network. It has been shown (44) that the coagulum

formed when blood is made to flow through a closed circular loop of plastic tubing mounted on a rotator resembles a natural thrombus. In this system the unesterified long-chain saturated fatty acids accelerate thrombus formation, while the polyunsaturated and shorter chain fatty acids are inactive. More information is needed about the relationship between clotting and thrombosis before a decision can be made concerning the part played by dietary fat and lipemia in the mechanism of thrombosis.

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The role of endocrines, stress, and heredity on atherosclerosis¹

L. N. KATZ

R. PICK²*Cardiovascular Institute, Michael Reese Hospital and Medical Center, Chicago, Illinois*

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Summary

ATHEROSCLEROSIS, manifested in the lipid-containing intimal lesions of small and large arteries, is the most common pathological form of vascular disease and the most detrimental in its effect on the blood and oxygen supply to any given organ. It is one form of arteriosclerosis, the most important one, leading to widespread morbidity and mortality in man in our Western civilization.

Several investigative approaches have led to the

conclusion, held by most but not by all workers in the field, that it is a disease primarily due to disturbance of the metabolism of lipid, lipoprotein, or cholesterol, or all three (72). Whether atherosclerosis develops into a major health problem within a population depends to a large extent on the life-span pattern of its diet. As early as 1934, Rosenthal (133) established that in no population with a high intake of fat and protein from animal sources is atherosclerosis absent, while populations subsisting on a diet low in animal fat and protein are uniformly free from the disease anatomically and, therefore, from the sequelae which produce morbidity and mortality. These findings have been amply confirmed in recent years by worldwide epidemiological studies (42, 74, 79, 107, 157). A tangible concomitant of the ingestion of a diet rich in saturated fats and cholesterol is a hypercholesterolemic tendency in a population. Thus, while the mean serum cholesterol level of the atherosclerosis-free populations is 150 to 180 mg per cent, the level for clinically healthy men of comparable age in the United States is 220 mg per cent (74). It is also a well-accepted fact today that serum cholesterol level is the most closely related single factor determining an individual's risk of developing clinical atherosclerotic coronary disease, i.e., the higher the serum cholesterol, the greater is the risk (30).

According to our present knowledge, the mode of action by which a diet rich in fats, particularly saturated fats and cholesterol, acts to influence lipid metabolism and to produce atherosclerosis can be summarized as follows: cholesterol synthesis in the

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liver is finely attuned to the amount of ingested cholesterol (61). This homeostatic mechanism is disturbed or may even be exhausted by a high-fat, high-cholesterol diet over the life span. This could explain the slowly increasing serum cholesterol levels with aging in our population. Recent findings also suggest that cholesterol synthesis by extrahepatic tissues, not regulated by dietary intake, may contribute significantly to the development of hypercholesterolemia and, therefore, atherosclerosis (1). Animal experiments lead us to suspect that the daily pattern of eating, the number of meals, for example, may help to determine the metabolic fate of the constituents of a potentially atherogenic diet (28).

In the case of a particular individual, the tendency to develop this increase in blood cholesterol and to acquire vascular disease will be subject to many factors other than the nature of the diet (73, 114). These other factors per se do not actually produce or prevent atherosclerosis, but they are capable of influencing it in the presence of a potentially atherogenic diet. Those which will be considered in this chapter are: *a*) the endocrines, *b*) heredity, and *c*) stress. They are the most significant ancillary factors so far known.

Because of discrepancies between the amount of anatomical vascular disease and the occurrence and magnitude of organ involvement, doubt has recently been expressed as to the relationship of atherosclerosis and, for instance, coronary heart disease (129, 163). However, no evidence is available that ischemic heart disease and ischemic disease of the brain, the extremities, or other organs occur without vascular disease (except on rare occasion). The major exception is one in which, with only minimal atheroma formation, it is possible to produce experimental coronary and renal thrombosis, and myocardial and renal infarction in rats (63), but even here vascular abnormalities were produced only in the presence of a high saturated-fat diet.

It is safe to state that without the basic arterial process of atheroma no morbid consequences would exist except as a rare phenomenon. Equally well documented is the fact that even with moderate and severe atherosclerosis no such morbid or mortal consequences need occur. These findings clearly point out that in atherosclerosis research we have to deal with two major questions: 1) What produces the basic vascular lesions? 2) What factor or factors may lead to the complications—ulceration, thrombosis, hemorrhage into a plaque that will ultimately determine the clinical fate of an individual? It is

possible that the same factors may determine both aspects. For example, prolonged hyperlipemia and hypercholesterolemia produce lipid deposition and atheroma in the arteries, and these blood changes also facilitate blood clotting, so that after an atheroma has developed in this fashion the stimulus is there to give rise to subsequent thrombus formation. Similarly, different neurogenic or hormonal factors, or both, may conceivably influence both processes. However, their effect may be preferential upon one or the other of these two stages. It must also be remembered that the vascular wall as an organ is capable of synthesizing cholesterol in small amounts and phospholipids in larger quantities (170, 183). Furthermore, it has been shown that species differences exist in the O₂ uptake between normal and atherosclerotic aortas, the O₂ uptake being higher in susceptible species and in atherosclerotic specimens (173). Permeability of the vascular endothelium is another factor that may be influenced by metabolic alterations due to hormonal, genetic, or stressful circumstances mediated by hormone release. Electron microscopy has confirmed the concept that lipids are being deposited in the intima by permeation from the blood stream (159).

Furthermore, differences in the responses of the vessels in different vascular beds to hormonal and other influences must not be overlooked. Whether these differences are due to the particular metabolism within the organ, to the nervous influences acting upon it, or to anatomical differences—possibly due to genetic factors—is not known at present. Some evidence for each of these causes is available (83, 94, 138).

Whether a given duration and intensity of hyperlipemia and hypercholesterolemia will or will not lead to the emergence of atherosclerotic disease, either in the form of the anatomical substrate alone or accompanied by the associated sequelae, is determined by the genetic make-up of the individual and very likely also by the nature of the environmental conditions under which he lives out his existence. Emotional factors, dependent in part upon genetic make-up and in part upon external environment, have recently been implicated in aberrations of lipid metabolism, in the genesis of atherosclerosis, and in the transformation of a silent vascular disease into a clinically overt one. Whether emotional states operate through hormones, or by way of the autonomic nervous system, or both, is not known at present. It is possible that hormonal and nervous factors themselves produce the emotional upsets as a

side effect independent of their direct actions upon atherosclerosis and ischemic disease. It is more likely, however, that emotional upsets induce hormonal and nervous factors which lead to ischemic disease.

It is thus apparent that any attempt to understand the pathogenesis of the multifaceted process of atherosclerosis requires that many factors be considered. In considering them, the effects of each on lipid metabolism, on the vascular wall, on blood coagulation, and on fibrinolysis have to be studied separately, and after that all the facts must be integrated to reconstruct the whole complex process. At present there are many gaps in our knowledge which are difficult to bridge. While the influences of hormones and heredity on lipid metabolism and on the vascular wall have been studied to some extent, their influences on blood clotting and fibrinolysis are poorly understood at present, since such studies are still in their infancy. Equally scanty is our knowledge of the effect of emotional factors on atherosclerosis and its sequelae.

HORMONES

That hormones influence lipid metabolism and atherosclerosis has long been suspected from clinical findings. Several diseases of endocrine organs show alterations in serum lipid levels and are associated with significant deviations in the incidence and severity of atherosclerosis. Several hormones are also known to affect the morphologic characteristics of the ground substance of the vascular wall and its cell membrane permeability. This would indicate that hormones may influence atherosclerosis either by a direct action on the vascular wall or through their influence on lipid metabolism (synthesis, absorption, transport, storage, excretion, and destruction), or both. The recognition of these factors stimulated extensive research into the mechanism of these actions. Only the action of the following hormones will be considered here: *a*) thyroid, *b*) pancreas, *c*) adrenal and pituitary, and *d*) sex. The part played by others is too poorly understood and too unimportant to warrant discussion.

Thyroid

The effect of thyroid hormone on lipid metabolism, particularly cholesterol metabolism, has been studied extensively in man and in various species of experimental animals. Endogenous thyroid hypersecretion,

as occurs in thyrotoxicosis, and the exogenous administration of the hormone have identical effects and will be discussed together. Different forms of hypothyroidism, whether primary or secondarily induced in man and animals by surgical thyroidectomy or by I^{131} administration, also show similar effects. The suppression of thyroid hormone secretion by thiourea drugs shows—in rats at least—a greater effect on cholesterol metabolism than that produced by the other methods of inducing hypothyroidism (22, 62).

Hyperthyroidism decreases serum cholesterol levels in man and animals. Recent tracer studies indicate that thyroid hormone increases synthesis of cholesterol in the liver, particularly of the free cholesterol fraction, and also increases catabolism and fecal excretion of this sterol (cf 22). Boyd (22) found in rats that neither exogenous thyroid hormone nor active thyroid hormone analogues lower normal serum cholesterol levels appreciably; however, if animals are made slightly hypercholesterolemic by dietary means, then these hormone preparations depress the dietary hypercholesterolemia. It has been demonstrated that this action of thyroxine or thyroid hormone is not due to the increase in basal metabolic rate per se, as several thyroxine analogues show the cholesterol depressant action without increase in basal metabolism (21). Furthermore, in chicks it was shown that dinitrophenol, a drug that increases basal metabolism, has no effect on serum cholesterol levels (148). Thyroid hormones also reduce β -lipoprotein concentration and that of certain classes of high density α -lipoproteins (70).

Hypothyroidism in man and animals produces a decreased synthesis of cholesterol while the biological half-life of serum cholesterol is increased and fecal excretion is reduced (22). The effect of hypothyroidism on lipoproteins is the direct opposite of the effect of exogenous thyroid hormone administration, i.e., it causes an increase in β -lipoproteins.

Pituitary thyroid stimulating hormone is without direct effect on cholesterol metabolism and atherosclerosis.

Thyroid hormone also affects the vascular wall. This has long been established in the older literature. Large doses of thyroxine or desiccated thyroid cause damage to the vascular media. They produce necrosis and calcification, similar to the changes produced by catecholamines (10). These are arteriosclerotic changes, not atherosclerosis. Smaller doses of thyroid hormone preparations have been shown to reduce cholesterol-oil-induced hypercholesterolemia and

atherosclerosis in rabbits (164). In chicks, larger doses of these hormones always depress diet-induced hypercholesterolemia; however, the effect on the vascular lesions is inconstant and inconsistent (152, 154). This may be due to the second action of the thyroid in producing vascular damage, providing a favorable site for lipid deposition and atherosclerosis.

In contrast to the inconsistent effects of excess thyroid hormones, the deficiency of the hormone (hypothyroidism) always produces increased atherogenesis in animals on a potentially atherogenic diet. This has been shown in chicks (154), rats (178), rabbits (165), and monkeys (146). Dogs develop atherosclerotic lesions only when a high-fat, high-cholesterol diet is combined with hypothyroidism (158).

No information is available at present indicating an effect of thyroid hormones on blood coagulation or fibrinolysis.

It can be concluded from all available data that thyroid hormone has a significant and important effect on cholesterol metabolism. The direct effect on atherosclerosis is undetermined and questionable. The continuing effort to separate calorogenic from hypocholesterolemic effects in thyroid analogues ultimately may alter the utility of thyroid preparations as antiatherogenic substances.

Pancreatic Hormones

Studies in man and in experimental animals indicate that two hormonal systems in the pancreas are actively involved in lipid metabolism and, therefore, in the control of the circulating serum lipids. These can operate independently or, more often, in an interrelated manner.

Knowledge of the two hormonal systems of the pancreas in man has been derived from the study of pancreatitis and diabetes mellitus. In addition, pancreatic enzyme systems are known to influence absorption from the upper digestive tract. Elastase, presumably a pancreatic enzyme, by influencing the elastic tissue in the media of the blood vessels, can change wall permeability and thus modify calcium and lipid deposition in the intima (82).

CHRONIC PANCREATITIS. Chronic pancreatitis in man with hyperlipemia and xanthomatosis, without diabetes, was first described by Wiesel (175) in 1905. Binet & Brocq (15) in 1929 reported a transient hyperlipemia and hypercholesterolemia in dogs with experimental pancreatitis. An antifatty liver sub-

stance high in bound choline was prepared from the pancreas of dogs by Dragstedt (34, 35). Adlersberg and co-workers carried out the most recent studies on experimental pancreatitis in dogs and rabbits, and also studied chronic pancreatitis in man (7, 167). He described the serum changes as consisting of a two- to three-fold increase in cholesterol and phospholipids with a four- to ten-fold increase of total lipids, the triglycerides, rendering the serum lactescent. The mechanism producing these serum lipid changes has not been clarified. An action by way of the enzyme system affecting lipid absorption has to be considered. Also destruction of the α -cells of the islets of Langerhans and their glucagon content may be involved (26). The elevation of triglycerides is considered the primary change leading secondarily to hypercholesterolemia and hyperlipemia by others (47). The significance of these findings in the pathogenesis of atherosclerosis needs further study.

DIABETES MELLITUS. The grossly and significantly increased incidence of atherosclerosis in individuals with diabetes mellitus has led to numerous clinical and experimental studies on the influence of the hormones of the islets of Langerhans, particularly insulin, on carbohydrate and lipid metabolism and on atherosclerosis.

The morphology of the arterial lesions in the diabetic does not differ from that in the nondiabetic. The difference between the two, then, is quantitative. However, in diabetes mellitus a characteristic capillary lesion in the retina and the kidney is found, consisting of capillary microaneurysms. Changes in serum lipids and complex carbohydrates are usually found when capillary lesions are present.

Severely atherosclerotic diabetic patients frequently show distinct disturbances of lipid and lipoprotein metabolism, including hyperlipemia, hypercholesterolemia, hyper- β -lipoproteinemia, and a marked elevation of esterified fatty acids (5, 16). They also have increased levels of serum polysaccharides. In diabetic acidosis and ketosis marked hyperlipemia and hypercholesterolemia are present, in addition to hyperglycemia. Insulin treatment results in bringing all three abnormalities toward normal. However, insulin given to normal individuals has no cholesterol-lowering effect (20).

Experimental studies on the effect of diabetes mellitus and of insulin on lipid metabolism and atherosclerosis have been carried out on numerous animal species, including dogs, rabbits, rats, and chicks. In all animals tested, diabetes produced by

alloxan injections or by pancreatectomy failed to cause atherosclerosis. When experimental diabetes was combined with cholesterol-fat feeding, atherosclerosis incidence was not higher than in normal animals on the same diet. Of particular interest are the findings by Duff *et al.* (38), who showed a decreased atherogenesis in diabetic rabbits on a cholesterol-oil diet. This trend was reversed when the animals were treated with insulin. These workers attributed this effect to the particular serum lipid picture developing under these circumstances. Alloxan diabetes produced a marked hyperphospholipemia with hypercholesterolemia and an increase in serum neutral fat. These animals, therefore, had a low ratio of total cholesterol to phospholipids (C/P ratio) in the hypercholesterolemic state. This particular lipid picture is usually accompanied by a low incidence and severity of vascular lesions. Insulin given to these rabbits caused the lipid picture to change so as to resemble the usual pattern obtained by cholesterol-fat feeding alone, namely a marked hypercholesterolemia with a mild hyperphospholipemia. This, in turn, resulted in an elevated C/P ratio and the attendant increased incidence and severity of atherosclerosis.

Interesting results were also obtained in studies of the pancreas and atherogenesis in chicks (154, 156). Pancreatectomized birds show no overt signs of disturbances of lipid or glucose metabolism. However, latent disturbances can be detected when these birds are given a high-cholesterol, high-fat diet or when adrenal steroids are administered. On this diet they show enhanced hypercholesterolemia and atherosclerosis, as well as retarded healing of lesions. With glucocorticoids they show a definite hyperglycemic response which is much greater than occurs in normal animals given these steroids. Cholesterol-fed, steroid-diabetic chicks do not show increased atherogenesis. Insulin, in hypoglycemic doses, when given to normal chicks does not increase the atherogenic potential of a high-cholesterol, high-fat diet. However, in these same doses insulin prevents regression of coronary artery lesions when it is given to chicks which are first made atherosclerotic and then placed on a plain, nonatherogenic diet—a diet which by itself normally leads to rapid regression of these early coronary lesions. The mechanism by which insulin prevents regression, while at the same time appearing to be without effect during the induction phase, is not clear. Large doses of insulin were used in these experiments, and this did cause marked hypoglycemia which in some way acted in a detrimental manner.

Also, the insulin probably increased the secretion of catecholamines and corticoids, as evidenced by the occurrence of periods of reactive hyperglycemia. Furthermore, some recent observations indicate that chronic insulin administration may produce prolonged hyperglycemia after the drug administration is discontinued, indicating some profound hormonal derangement. Local effects within an atheroma also cannot be excluded.

How much of the effect of diabetes mellitus or insulin on atherosclerosis is due to the changes in lipid metabolism and how much to factors influencing the vascular wall is not clearly established. Furthermore, several authors (32, 84) have suggested that in diabetics, and even in nondiabetic members of their families, the ground substance of the vascular wall is subtly changed, making it particularly prone to atherosclerosis. In addition, blood coagulation is changed in uncontrolled diabetes as in other hyperlipemic states.

From all this it is apparent that the increased tendency of the diabetic to develop atherosclerosis must depend on a number of factors.

Adrenal and Pituitary Hormones

Adrenal cortical and medullary hormones have been shown to influence lipid metabolism and the vascular wall. However, the lipid metabolic responses to these hormones differ among the several animal species studied, including man. Also, their acute and chronic effects on circulating serum lipids differ. The mechanism of their action has not been satisfactorily elucidated.

ADRENAL CORTICAL HORMONES AND ACTH. Hyperactivity of the adrenal cortex in Cushing's disease is frequently associated with hypercholesterolemia and hyperlipemia and a tendency to severe premature atherosclerosis (64, 68, 177). In contrast, bilateral destruction of the adrenals in Addison's disease is accompanied by low serum cholesterol levels (142). Furthermore, the adrenal cortex has a high cholesterol content and it can synthesize and discharge cholesterol and steroid hormones readily (147, 174).

Adrenalectomized dogs maintained on desoxycorticosterone acetate (DCA) show a marked decrease of serum cholesterol and phospholipid levels (31, 182). When cortisone is substituted for DCA, a marked rise in these lipids occurs. Combined DCA and cortisone administration showed no further increase over cortisone alone. It was concluded from these studies

that the primary effect on circulating lipids is due to cortisone (31, 182). It has to be borne in mind, however, that data derived on adrenalectomized animals are complicated by the fact that simultaneously with the depletion of cortical hormones there is also a lack of medullary catecholamines, and these, too, have an effect on lipid metabolism.

Aldosterone, the adrenal hormone affecting electrolyte metabolism, apparently has no effect on the circulating lipids, but may affect the vascular wall according to some recent data (80).

The pituitary adrenocorticotrophic hormone (ACTH) has an effect similar to, but less marked than, cortisone. In man, the administration of either cortisone or ACTH produces an initial depression of serum cholesterol levels with a subsequent rise on continued administration (144). In the dog, the response of the serum lipids to corticosteroids, particularly cortisone, is relatively mild. In the rabbit and the rat, the effects of ACTH and corticosteroids are qualitatively similar but much more pronounced. The serum cholesterol elevation resulting from cortisone treatment is especially marked in the free cholesterol fraction. Phospholipids are elevated concomitantly, resulting in a normal C/P ratio, despite elevated cholesterol levels. Triglycerides are also increased, rendering the serum lactescent (7). In the chick, the active steroid is 17-hydroxycorticosterone (compound F). It has lipid effects similar to those described in the rabbit for cortisone.

Atherosclerosis has not been induced in dogs, rabbits, or chicks by the administration of adrenal cortical hormones despite the lipid changes they produce. If these steroids are given in the presence of an atherogenic diet, the effect on the circulating lipids is variable depending upon the species, but the effect on atherogenesis is similar—corticoids depress cholesterol-induced atherogenesis.

It has been postulated that the atherosclerosis-depressing action of these steroids is due to their decreasing the permeability of the vascular endothelium. Adlersberg's group has shown that when hyaluronidase—a substance which increases cell permeability—is given simultaneously with cortisone the atherosclerosis-inhibiting action of the corticosteroids is overcome and atherosclerosis proceeds as in the controls (166).

Some authors produced increased arteriosclerosis and secondarily atherosclerosis by the administration of ACTH in rats (171, 172) and dogs (100). It is possible that these effects are due to the action of the

hormone on the vascular ground substance (mucopolysaccharides) and fibroblasts (102).

No specific data are available implicating the adrenal cortical hormones in blood coagulation or clot lysis.

ADRENAL MEDULLARY HORMONES. *l*-Epinephrine is the adrenal medullary hormone most extensively studied. It influences lipid metabolism and produces damage of the vascular wall in the form of medial necrosis and calcification. The other catecholamines probably act in a similar manner. Both of these actions of *l*-epinephrine may produce arterio- and atherosclerosis. In addition, *l*-epinephrine, being a pressor agent, may further increase atherogenesis due to the arterial hypertension which ensues on chronic endogenous overproduction or by protracted exogenous administration of the hormone (126).

In the older literature disparate data on the circulating lipids after catecholamine administration have been described. Some observers noted a transient hyperlipemia, probably due to an action on mobilization and transport (33, 45, 60, 71). Others observed a decrease in serum cholesterol, phospholipid, and total lipids (39, 71). Recently, Shafrir *et al.* (143) clarified some of these discrepancies. They showed that a single subcutaneous injection of *l*-epinephrine in dogs produces a prompt, transient elevation of serum-free fatty acids and a delayed elevation of β -lipoproteins. Prolonged daily *l*-epinephrine administration, however, produced a marked increase in cholesterol levels, with a smaller concomitant rise in phospholipids. This epinephrine reaction was abolished by adrenalectomy and restored by cortisone treatment.

ANTERIOR PITUITARY HORMONES. Pituitary growth hormone (somatotropin) influences lipid mobilization and transport as well as the distribution of lipid between the liver and fat depots (85). Information on the influence of this hormone on circulating serum lipids is scant and the effects are variable in different species. However, this may be due, in part at least, to the fact that there are differences, both physiological and chemical, in the nature of growth hormone preparations obtained from different animal species (19). Some stimulation of fibroblast growth with this hormone has been described (102). No data are available indicating any possible effect of this hormone on atherogenesis.

Recently, Rudman *et al.* (134) demonstrated the existence of a separate and distinct hyperlipemia-producing hormone of the anterior pituitary.

CONCLUSION. All these studies would suggest that the adrenal and pituitary glands have a significant influence on lipid metabolism, but the exact mechanism of these effects is still poorly understood. They also affect the metabolism of the vascular wall and may, therefore, be intimately related to atherosclerosis. Whether they have a direct effect on blood coagulation and clot lysis has not yet been explored. Some effects attributable to nervous and emotional factors may actually be related to the release of adrenal hormones under these circumstances. Further studies of these hormones should be conducted.

Sex Hormones

Numerous clinical and experimental studies indicate a profound influence of male and female gonadal hormones on lipid and lipoprotein metabolism and atherosclerosis. Also, it has been reported that these hormones exert a marked influence on ground substance and connective tissue elements as well as a slight, less well understood, effect on the clotting mechanism. The influences of female sex hormones are more pronounced than those of the male hormone, and the effects of the male and female hormones are in general opposite and antagonistic.

The levels of circulating lipids and lipoproteins in normal males and females of all ages have been extensively studied (6, 96, 135). Up to the age of 20 years, total cholesterol and phospholipid levels are similar in the two sexes. Both these lipid fractions rise significantly in men up to the age of 33, and then remain stable up to age 60. In women, on the contrary, they stay constant up to the age of 32, and from then on a steady rise occurs until 58 years of age. The 1:3 ratio of free to esterified cholesterol is fairly constant in both sexes at all ages.

Serum lipoprotein patterns show a distinctly sex-linked difference, as does the cholesterol content in the different lipoprotein fractions. Young women have more α -lipoproteins and α -lipoprotein cholesterol than men of all ages, postmenopausal women, or castrated women. Oliver & Boyd (110, 111) studied lipids and lipoproteins during the menstrual cycle and during pregnancy and found a depression of β -lipoproteins and of the cholesterol/phospholipid (C/P) ratio coincident with the peak of estrogen secretion at ovulation. During the third trimester of pregnancy β -lipoproteins and the C/P ratio increase despite large estrogen secretion. These contradictory findings need clarification.

Sex differences in serum cholesterol levels are also

observed in animals. Female rats have higher serum cholesterol levels than males (22). Egg-laying hens and pigeons have elevated serum cholesterol levels with very high phospholipid levels and, therefore, significantly depressed C/P ratios.

The normal lipoprotein pattern of the chick differs from that of man and most mammals in that the main component is α -lipoprotein (151). Furthermore, giving estrogens to the cockerel elevates β -lipoprotein, instead of α -lipoprotein as in man (151). Incidentally, the effect of diet on lipoprotein levels in chicks is also opposite to that seen in man.

In man, androgens increase β -lipoproteins and serum cholesterol. Eunuchs have lower cholesterol and β -lipoprotein levels than normal men (52).

Estrogen administration to men or postmenopausal women changes the serum lipoprotein pattern to the young female type and this pattern remains as long as therapy is continued, even over several years (151, 155). The effect on serum cholesterol is not so uniform. Several authors described a fall (7, 110), while others found no change (151, 155). However, there is uniform agreement that the phospholipid level rises and therefore that the C/P ratio falls.

Androgens even in small doses, given to men concomitantly with estrogens, counteract the estrogenic serum lipid effect without counteracting the feminizing effect on the secondary sex characteristics. The latter action represents one instance where the action of the two hormones is not antagonistic, at least in man.

The mechanism by which the gonadal hormones influence lipid metabolism is not yet entirely clarified. Boyd (22) carried out tracer studies with C^{14} -labeled acetate in rats and found that estrogens slightly depress plasma cholesterol synthesis and significantly reduce the biological half-life of cholesterol. Ovariectomy in female rats had the opposite effect (22, 44).

Furman *et al.* (53) have shown an interrelationship of methyltestosterone and dietary protein intake on serum lipoproteins in men. On a low-protein or protein-free formula diet both α - and β -lipoproteins were significantly depressed, beyond the depression of the protein-free diet alone. These findings have been confirmed by Olson & Vester (115).

A very definite action of the sex hormones, particularly the estrogens, on atherosclerosis has also been established. Data from clinical medicine are suggestive, experimental data on animals are indicative.

Premenopausal women have less gross coronary atherosclerosis than men or castrated women (127, 181) and a markedly lower incidence of myocardial

infarction (113, 130). After the menopause the incidence of myocardial infarction in women slowly rises to become almost equal to that in men by the eighth decade (110, 113). Furthermore, Marmorston *et al.* (99) have shown that postmenopausal women with coronary artery disease have lower urinary estrogen levels than healthy women of the same age, and also have lower levels of protein-bound iodine indicating a decreased thyroid function. Bersohn & Oelofse (14) made similar observations in man. Aortic atherosclerosis shows no significant sex difference (43, 128, 176). The protection of the female from coronary atherosclerosis is lost in the presence of familial hypercholesterolemia and in diabetes mellitus.

Cockerels on a high-fat, high-cholesterol (atherogenic) diet are protected against coronary atherosclerosis when given estrogens (119). Also, previously induced atherosclerosis can be completely reversed by the hormone (120). Aortic atherosclerosis is not influenced. Sexually mature, estrogen-secreting hens fed the atherogenic diet develop aortic atherosclerosis but no coronary atherosclerosis (150). Castration of these hens makes them susceptible to coronary lesions (121). Estrogens given to chicks on a normal non-estrogenic diet induce aortic atherosclerosis, but not coronary atherosclerosis (27, 67, 86). These different effects of estrogens on coronary and aortic atherosclerosis are a good example of the previously stated observation that local anatomic or metabolic factors are of importance in atherogenesis. This makes it imperative for the investigator to study the several vascular beds separately, and not to draw the conclusion that observations made in one vascular bed necessarily apply to other parts of the arterial tree.

Freedom from coronary lesions in chickens is accompanied by the previously described characteristic serum lipid changes resulting in a normal C/P ratio in the presence of hypercholesterolemia. The same effect on lesions and lipids was obtained in rats (108). In male rabbits neither serum lipid changes nor coronary protection can be achieved by estrogen administration (151). Ludden *et al.* (91) observed that both androgens and estrogens protect intact female rabbits from cholesterol-induced aortic atherosclerosis. Neither hormone was effective in males or in castrated females.

Another exception to this sex phenomenon is atherosclerosis in a susceptible strain of pigeons (*vide infra*). Old, egg-laying pigeons show coronary atherosclerosis despite the usual low C/P ratio characteristic for female birds (66, 88-90).

Androgens in large doses depress diet-induced

hypercholesterolemia without influencing atherosclerosis (123).

Studies in chicks revealed that estrogen protection is preserved even if estrogen administration is combined with androgen administration or with administration of DCA or compound F, or is used after pancreatectomy (149, 154). The only clear-cut reversal of the estrogen effect was obtained when chicks were made hypothyroid by the administration of thiouracil (122). A slight decrease of estrogen reversal of previously induced lesions was observed when insulin was administered concomitantly with estrogens during the period when the lesions were regressing (154). Recently,³ we have noted that blocking the reticulo-endothelial system also prevented the estrogen effect.

Estrogens have also been shown to stimulate growth of ground substance, particularly collagen and fibroblasts. They also stimulate the reticuloendothelial system (18, 25). Furthermore, there is some indication that estrogens influence fibrin content and fibrinolytic activity of the blood (11, 56, 57). It has also been reported that intravenous injection of estrogens, particularly conjugated equine estrogens, has a hemostatic effect (58).

An indication that the local influence of estrogens on the vascular wall may be related to atherosclerosis was recently obtained in chicks. It was shown that atherosclerotic abdominal aorta and coronary lesions, produced by a high-fat, high-cholesterol, low-protein diet, can ulcerate if large doses of estrogens are given (76). In the chick this was shown to occur as a stage in the healing process of these lesions. This is the first suggestion that estrogens may also influence the vascular wall of the aorta.

The action of estrogens on lipid metabolism and atherogenesis stimulated several long-term research projects in man using different female sex-hormone preparations in the therapy of patients with proven ischemic heart disease (101, 112, 131, 151, 155). The results show a possible life-prolonging action only when a natural estrogen preparation (conjugated equine estrogens) is being used. It is not known why this difference exists between natural and synthetic compounds. The therapeutic value of this regimen is, however, limited by the accompanying feminizing action of the hormone. Several nonfeminizing estrogen

³PICK, R., L. N. KATZ, P. J. JOHNSON, AND D. E. CENTURY. The role of the reticulo-endothelial system and estrogens on coronary atherogenesis in cholesterol-fed cockerels. *Circulation*. In press. (October 1952.)

derivatives are being explored, so far without worthwhile results.

From all these data it is evident that gonadal hormones have a significant influence upon lipid metabolism and atherogenesis.

HEREDITY

That genetic or hereditary factors may influence the development of atherosclerosis is suggested by animal experimental and human studies. It has to be emphasized, however, that these tendencies become evident only in the presence of a potentially atherogenic diet. If the environment is favorable, genetic tendencies may not become evident. As in many other diseases, the interplay between host and environment is of the utmost importance.

Animal experiments have indicated species differences in the susceptibility of atherosclerosis. Man and several species of birds develop atherosclerosis spontaneously (51). Also old dogs, kept as pets, have been found to exhibit aortic and coronary atherosclerosis (87). Most animals, however, living in their natural environment do not exhibit vascular lesions, with the possible exception of the baboon (55, 93) which shows fatty streaks in the aorta.

Species differences are also found in the response to high-level cholesterol-fat feeding. Chicks and rabbits respond to this regimen with severe hypercholesterolemia and atherosclerosis in a short period of time (10, 72). It is more difficult to produce similar effects in ducks, guinea pigs, and hamsters (8, 9, 59). In the dog, cholesterol feeding has to be combined with suppression of the thyroid activity in order to produce both lipid and vascular changes. In the monkey, cholesterol feeding has to be combined with a deficiency in sulfur-containing amino acids in the diet to produce lesions (98). Recently, however, atherosclerosis was induced in rhesus monkeys by a high-saturated fat, high-cholesterol, nondeficient diet alone (29). In the rat, the species most resistant to the induction of atherosclerosis, this disease has been produced by a combination of multiple dietary and hormonal manipulations, i.e., cholesterol, cholic acid, and saturated fat in the diet, plus hypothyroidism and unilateral nephrectomy (63).

The cause of these species differences has not been entirely clarified. Recent tracer studies, however, indicate species differences in cholesterol synthesis, turnover, and degradation rates, and in the handling of dietary cholesterol (61, 62). Other studies indicate

differences in the number of vasa vasorum in the aorta—richest in resistant species and poorest in the very susceptible (139). Whether or not these species differences are the actual cause of the varied susceptibility to hypercholesterolemia and atherosclerosis is not known. Nor is it known how they are inherited.

More significant perhaps than species differences, are strain differences which occur within a single species. These have been demonstrated in rabbits (145). In chicks they have been described by Opdyke & Ott (116) and others (46). They have been indicated in dogs (100). The most recent and thorough investigations into strain differences was carried out by Lofland & Clarkson (88, 89, 90) who have studied several breeds of pigeons, in particular: the White Carneau, the White Racer, and the Autosexing King. The first shows severe aortic and some coronary atherosclerosis in old birds of both sexes kept on a low-cholesterol, low-fat commercial diet. The second strain does not show any lesions on the same diet. The third, genetically a cross-breeding between the first two, has intermediate incidence and severity of lesions. The onset of atherosclerosis in response to high cholesterol feeding of the three breeds parallels the severity of the spontaneous lesions. All three breeds spontaneously have high serum cholesterol levels, around 400 mg per cent, with marked seasonal variations (66), and resemble one another in many of the biochemical aspects studied by these authors. Wherein lies the definitely genetic difference in the production of lesions is unexplained.

In man, it has often been suggested that genetic and hereditary factors may play a role in lipid metabolism and coronary atherosclerosis. The first indication of such a relationship was described in 1930 (65). A vast literature on statistical and genetic investigations has since appeared proving the familial occurrence of a xanthomatous tendency, i.e., a tendency for hypercholesterolemia and atherosclerosis to appear in families. This was reviewed recently by McKusick (94). The most extensive clinical studies were carried out by Adlersberg *et al.* (2-4) and by Thomas & Cohen (161). Some limited studies are available on the incidence of these disorders in identical and fraternal twins, living together or separately, which may aid in determining the respective roles of heredity and the environment (118).

Adlersberg and others (3, 17, 40, 137, 161) consider hypercholesterolemia an inborn error of metabolism, probably inherited as an "incomplete" dominant trait. Familial hypercholesterolemic xanthomatosis, a disorder of lipid metabolism characterized

by the triad: hypercholesterolemia, cutaneous or tendon xanthomata, and severe premature atherosclerosis (sometimes occurring even in childhood), is the most severe stage of this inherited disorder. It is probably homozygotic. A hypercholesterolemic tendency without xanthomata also occurs; this milder form is heterozygotic (3). Recently, Epstein *et al.* (41), restudying the families originally published by Adlersberg, re-emphasized the interplay between genetic tendency and the environment. C. B. Thomas, in her study of the families of healthy medical students, showed a definite trend for the offspring of parents with hypertension and or coronary artery disease to have more hypertension and coronary disease than children of parents not so afflicted. If one parent had either of these diseases the occurrence among the offspring was intermediate. Also, she reported a fourfold greater frequency of occurrence of coronary artery disease among the siblings of the afflicted parents than among siblings of parents not so afflicted. She concluded that the gradation of the disorder rates were consistent with the Mendelian law of inheritance. However, she could not exclude a multiplicity of genetic factors and associated modifying environmental agents.

Whether genetic and hereditary factors influence atherosclerosis also by determining the anatomical pattern of the circulatory tree, particularly that of the coronary circulation, is difficult to evaluate—but the possibility does exist (94).

In addition, the studies of Gertler & White (54) on young coronary patients have yielded information regarding body build. Even though no particular "coronary habitus" could be established, young patients with coronary disease as a group belonged predominantly to the mesomorph body build. Recently, attention has also been focused on personality and character traits, as well as the responsiveness of the autonomic nervous system, partially genetically determined, and their possible relationship to coronary disease proneness. But these interrelationships need further clarification (136).

No data are as yet available on the familial tendency to accelerated blood clotting and thrombus formation, other than the tendency of hyperlipemic serum to shorten coagulation time. However, it is not inconceivable that such genetic traits may be uncovered.

From the evidence presented it can be concluded that genetic and hereditary traits may be an important predisposing factor in an individual's response to dietary and environmental factors leading to athero-

sclerosis, anatomically and clinically. But this is still, for practical purposes, an uncultivated field of systematic study of great importance.

STRESS

In recent years, interest has grown concerning the possible influence of physical activity and psychological or emotional stress on the development of atherosclerosis. It has also been suggested that both of these types of "stress" may be involved in precipitating thrombosis or sudden occlusion of a blood vessel in which pre-existing but clinically occult disease is present. Further, such stress may act as the trigger mechanism in aggravating the ischemia of an organ, particularly of the heart and the brain, which already has a deficient blood supply because of an atherosclerotic process. The presence of atherosclerotic disease per se limits the ability of the circulation of an organ to adjust to augmented demands placed upon it.

As has been pointed out for other facets of the problem in previous sections of this chapter, "stress," too, exerts its role only in the presence of a life-span pattern of diet high in cholesterol and fat, particularly saturated fat. When this potentially atherogenic diet is absent, differences attributable to stress and other factors fail to appear. Therefore, differences in the incidence of clinical coronary disease according to occupation for instance, are found only in those populations in which the over-all incidence of this disease is high, presumably because of the dietary factor.

Physical Activity

Results from the animal laboratory with regard to the influence of enforced physical activity in the presence of an atherogenic diet are contradictory. Brown *et al.* (24) found no differences in rabbits. Kobernick & Niwayama (81), working with cholesterol-fed rabbits which were forced to exercise adequately by combining a mechanical treadmill with conditioning to electric shocks, found significantly less atherosclerosis in the exercised rabbits as compared to the sedentary controls—although the degree of hypercholesterolemia was similar in both groups. Brainard (23), working with rabbits exercised on a treadmill, found no differences in the amount of aortic cholesterol between the active and the sedentary group. Myasnikov (109) obtained positive results in the rabbit in favor of a protection of the

exercised group. However, he also found an increased incidence of myocardial infarction in the exercised group despite the decrease in gross aortic and coronary atherosclerosis. Serum cholesterol levels were found to be significantly lower in rats forced to swim than in sedentary controls and in pair-gained sedentary controls (69). Orma (117), Warnock *et al.* (168), and Wong *et al.* (180) reported that exercise decreased hypercholesterolemia and atherogenesis in cholesterol-fed cockerels. McAllister *et al.* (92), on the contrary, found more severe atherosclerosis in exercised, cholesterol-fed, hypothyroid dogs as compared to sedentary ones. Their findings are complicated by the fact that the exercised dogs were ingesting their rations as meals while the sedentary hypothyroid animals, with the usual depression of appetite, ate their food slowly over the entire 24-hour period. Such differences in feeding pattern in chicks have been shown to influence the atherogenicity of the diet per se (28).

Data in man relating physical activity to anatomical atherosclerosis or clinical coronary disease are even more difficult to evaluate. Several investigators (78, 97, 160) observed that increasing the caloric intake did not produce the expected increase in serum lipoprotein and cholesterol levels when the subjects were exercised intensely enough to prevent weight gain. They concluded that only a positive caloric balance over a long-time period could elevate serum lipid levels.

Pomeroy & White (125) reviewed the life history of former football players and found fewer deaths from cardiovascular disease among those who continued a program of regular exercise into the middle years than among those who stopped physical activity after their school years.

The most indicative data relating the amount of physical activity at work with a decreased incidence of death from atherosclerotic vascular disease, particularly ischemic heart disease, come from the studies of Morris in Great Britain (104, 106). His data were obtained from a relatively homogenous population of a similar socio-economic group: by a comparison of sedentary bus drivers with physically active conductors, by a comparison of sedentary telephone operators with active postmen, and by other comparisons of a similar nature. His findings indicate that the incidence of ischemic heart disease in middle age tends to be lower in the groups habitually engaged in a greater amount of physical activity. These investigations, although indicative, are not to be taken as final proof, because, in the bus

workers at least, there was a difference in obesity—the drivers were more obese from the start than the conductors, as judged by the size of the uniforms (103). This leaves open the question of whether the difference between jobs was fortuitous, dependent upon self-selection, which in turn was dependent on temperament and body build of the individual worker. Studies from other countries, i.e., Sweden, Finland, and Italy (74), with a generally high morbidity and mortality rate from atherosclerotic heart disease, are not so clear cut as the British studies. Studies from the United States show no difference between active and sedentary groups in an urban population (153, 157); however, farmers have less atherosclerotic heart disease than city dwellers. Some authors suggest that continued physical activity through middle age may be of possible benefit in the prevention of atherosclerotic disease (179).

One fact clearly emerges from these studies: that no difference between physically active and inactive groups can be observed in populations with a low incidence of atherosclerotic heart disease and low mean serum lipid levels. In populations with a high incidence, however, there is a difference in some but not in all countries. Furthermore, even where a difference has been well documented, as in Great Britain, this is only relative; the absolute incidence of this disease in the physically active is still high compared to all groups in a country with a low incidence. Therefore, physical activity must play a minor role compared to other factors such as diet.

The mechanism by which physical activity might influence atherosclerosis is not clear. The data regarding serum cholesterol and lipoprotein levels suggest an influence via metabolism. Other data also indicate that the factors preventing blood coagulation and aiding fibrinolysis are favorably influenced by heavy physical work (11, 12, 77). This was pointed out in human studies, and Warnock *et al.* (168) report the same effect in chicks. These latter effects may be important, particularly since Morris' work points to a decrease of coronary thrombosis and major occlusion in active middle-aged men, without any noticeable decrease in vascular atheroma and diffuse, nonfatal myocardial fibrosis (104).

Furthermore, physical work may have another effect. There are several studies indicating a stimulation of the production of intercoronary anastomoses by physical work (13, 105, 184). Nor must it be overlooked that physical activity is a form of training which permits the body to adjust more readily to periods of stress.

It is apparent that there is room for further studies of this important aspect of atherosclerosis.

Emotional Stress

A number of investigators have shown that emotionally stressful life situations transiently elevate serum cholesterol levels and shorten the blood-clotting time. This has been noted in medical students at the time of examination (36, 162), and Friedman *et al.* (48) observed it in accountants when they were under professional peak loads. Several other workers have published data linking the acute episode of coronary occlusion to immediately preceding stressful life situations (37, 136, 169). The proponents of the hypothesis that emotional stress influences atherogenesis and may precipitate clinical episodes of occlusion implicate the stresses of our modern mechanized civilization in particular. Emotional stress also produces elevation of blood pressure, and this in turn may have a deleterious effect on the vascular wall. In this and other ways hypertension favors atheroma formation.

The study of emotional factors in relation to cardiovascular disease is in its infancy. The main reason for the difficulties in the evaluation of this factor is the lack of an effective measure of emotional stress and of the various personality profiles (75). The mechanism by which psychological stress influences body homeostasis is also difficult to assess. It may operate: *a*) by disturbing endocrine balance, e.g., via pituitary-adrenal stimulation and catecholamine release (50, 95, 132, 140, 162), thereby influencing blood pressure, cholesterol metabolism, coagulation, and fibrinolytic activity; or *b*) by other, as yet unknown, mechanisms including an action via the nervous system. Numerous acute psychological episodes of this type over the life span may lead to the establishment of chronic changes, such as those which may operate in hypertension.

Experience from the animal laboratory is equally fragmentary. Cold stress was shown to produce coronary artery changes in rats (141). Friedman & Uhley (49) have shown that rats kept tense in anticipation of electric shocks showed significantly shortened blood-clotting time. They found no difference in coronary atherosclerosis between aggressive and passive chicks on an atherogenic diet. Other results confirm this observation. Recent studies in our laboratory indicate that isolation of chicks in a quiet, undisturbed room increases the atherogenic response to a high-fat, high-cholesterol diet (124).

Also, isolation during the healing phase of atherosclerosis prevents regression of lesions. Such isolated cockerels, in addition, showed retarded sexual growth as evidenced by decreased testis weight and comb size, as well as a decreased food efficiency expressed by smaller weight gain on a food intake similar to that of the controls.

It cannot yet be determined from these results whether the observed effects of isolation of the birds constituted a response to a severe stress, specifically the unnatural isolation, or were, on the contrary, the result of the lack of normal stresses. However, all these data indicate that certain environmental influences, mediated via the central nervous system and involving the nervous and hormonal regulation of body functions, including that of the vessels themselves, can influence the vascular response to a potentially atherogenic diet. These findings may have far reaching implications, particularly should "lack of normal stress" be the underlying cause.

The evidence relating emotional or psychological stress to atherosclerosis, clinical or experimental, is at best fragmentary. It is much too early to extrapolate the findings and to make any major generalization. Many further well-controlled and systematic studies are required to help our understanding of the complicated mechanisms which operate in this elusive area.

SUMMARY

From the data presented in this chapter the following conclusions can be drawn:

Whether or not atherosclerosis emerges as a major health problem in a population is largely and mainly determined by the life-span pattern of the diet. In the case of any individual member of a population group which is habitually ingesting a potentially atherogenic diet, several other factors will determine the degree and extent of atherosclerosis and clinical atherosclerotic disease—this is not always mirrored by the blood cholesterol or other lipid levels. There is a complex interplay between diet and these other factors which operate to accelerate or retard atherogenesis. The most important of these accessory factors determining the individual's fate with regard to atherosclerosis are hormones, heredity, and stress.

It is hopefully felt that by taking all these factors into account it will become possible to single out persons particularly prone to develop atherosclerotic disease at a relatively early age and to suggest dietary

or other measures for them, with the expectation that the development of atherosclerosis can be retarded, its sequelae avoided or delayed, and a clinical catastrophe prevented or put off for a variable time. Much work is still needed to reach this goal and many aspects of the problem are poorly understood at the present time. But progress is being made year by year in the multidisciplinary attack aiming to understand the pathogenesis of atherosclerosis, and seeking

to further its prevention and to improve its management once it develops.

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Peripheral vascular diseases— diseases other than atherosclerosis¹

GEORGE E. BURCH

JOHN PHILLIPS

*Department of Medicine, Tulane University School of Medicine,
and Charity Hospital of Louisiana, New Orleans, Louisiana*

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ONE OF THE GREAT INTERESTS in the vascular system is its reaction and response to disease. Although most

physiologic studies have been concerned with the normal state, the pathophysiology of vascular disease is of considerable importance to the physiologist and the clinician. Attempts will be made in this chapter to correlate the interactions of vascular malfunction with the pathologic lesions and their clinical manifestations. The presentation will be limited primarily to diseases of and observations on man.

In the discussions to follow the term "peripheral vascular disease" will refer to disease affecting largely the circulation to the limbs. This obviously excludes a discussion of disease in other circulatory beds; notable among these sites are the pulmonary, portal, renal, and cerebral vessels. Further, the discussions will be limited in large part to "primary" vascular disease, or disease states in which alterations in blood vessels and their function are the basic cause for the disease manifestations. Vascular changes associated with or secondary to primary disease in other organs are important but they are beyond the scope of this presentation. Examples of these secondary vascular disturbances are the spider angiomas and palmar erythema occurring in liver disease, aging, rheumatoid arthritis, and pregnancy; the pale avascular skin of castrate and eunuchoid men; the reddish flushes of the menopausal states; the cyanotic flushes of serotonin-producing carcinoids; the pallor of the nephrotic syndrome, hypothyroidism, and pituitary insufficiency; the vasoconstriction of pheochromocytomas; the vasodilatation of thyrotoxicosis; the vascular changes of acute exanthema, scarlet fever, and other infectious diseases; and the digital clubbing and cyanosis of cardiac and pulmonary disease.

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VASCULAR MALFUNCTION IN GENERAL

Vascular malfunction might be defined as that temporary or permanent condition which exists when the circulation fails to meet its intended functions of *a*) temperature regulation, *b*) tissue nutrition, and *c*) repair.

Malfunction might arise through active vasomotor or passive structural (anatomic) mechanisms. Vasomotor (not limited only to neuromuscular) mechanisms include *a*) increase in vessel tone ("vasotightening"), decrease in luminal cross-sectional area, or a combination of these (vasoconstriction), or *b*) decrease in vessel tone ("vaso loosening"), increase in luminal cross-sectional area, or a combination of these (vasodilatation). Vasomotor changes might be induced through neural mechanisms, humoral factors affecting any of the vessel wall coats, other unknown factors, or any combination of these. These reactions imply a degree of reversibility.

Structural or anatomic mechanisms by which vascular malfunction might occur are *a*) structural obstruction (occlusive), *b*) structural dilatation (aneurysm or varix), or *c*) abnormal vascular communications. These changes imply a degree of irreversibility.

Somewhat difficult to define as either active vasomotor or passive structural changes are vascular distention and vascular collapse (the latter not referring to the "shock syndrome"). Vascular distention or congestion implies a relative increase in vessel tone (as opposed to vasodilatation) but with an increase in luminal cross-sectional area. Vascular collapse implies a relative decrease in vessel tone (as opposed to vasoconstriction) but with a decrease in luminal cross-sectional area. These are, of course, potentially reversible states.

Structural diseases have been termed "organic," whereas the vasomotor diseases have been called "functional." Division of peripheral vascular diseases into organic and functional categories, although convenient, is purely arbitrary. Certainly, altered physiology has its structural counterpart. Means to resolve this artificial dichotomy then are dependent simply on the sensitiveness of methods for morphologic observations. In the past, the division of diseases from the anatomic standpoint has been dependent largely on light microscopy. Under existing classifications, for example, early and mild Raynaud's disease is a functional disorder. However, with the use of more sensitive methods such as electron

microscopy the same stage of the disease might be shown to be associated with structural defects whether it be in the vasculature itself or in the nervous system or in both. Thus, by present "policy" the disease is now considered both organic and functional.

Regardless of the above criticisms, it is still convenient for clinical purposes to classify vascular disease within organic or functional categories. This focuses attention on the more observable underlying mechanisms in the characteristic manifestations of the disease. With this in mind, more emphasis shall be placed here on the disorders in which altered physiology is the most readily detectable underlying mechanism; these diseases include predominately, but certainly not exclusively, the functional disorders. It should be remembered that none are purely organic or purely functional and that all vascular diseases have elements of each.

Changes which influence the circulation and its functions, although not directly arising from the vessel wall itself, pertain to such factors as blood volume, cardiac output, pulse rate, blood viscosity, sludging, blood gases, neurogenic and psychogenic disorders, endocrine and humoral factors, and many others. Many of these factors operate simultaneously to various degrees and with temporal variations. These topics are covered in other chapters of this volume.

APPROACH OF THE CLINICIAN AND CLINICAL PHYSIOLOGIST TO THE STUDY OF PATIENTS WITH DISEASES OF THE PERIPHERAL CIRCULATION

The clinical peripheral vascular physiologist has a difficult and complex task. He must observe the symptoms and clinical and laboratory signs in his subject which suggest the possibility of pathological alteration in the peripheral circulation. He must attempt to discover the underlying pathologic anatomy of the clinical manifestation. Most difficult of all, he must attempt to explain the observed changes in terms of pathophysiologic mechanisms, establish a diagnosis and then introduce corrective therapeutic measures based upon established pharmacodynamic and physiologic principles. This is done with an aim to modify the altered pathophysiology in order to establish as near normal vascular function as possible for as long a period of time as possible. This objective requires a satisfactory understanding of the normal and abnormal functions of the interrelated organ systems which may influence the diseased state. The clinician must attempt to estimate properly the

relative quantitative, qualitative, and temporal roles of the many contributing factors such as the numerous effects of disease of other organ systems. All of these factors must be carefully integrated in order to decide upon the type, amount, and time of administering various therapeutic measures.

Progress in the basic understanding of peripheral vascular disease has been slow. Because of the enormous number of variables and the complex nature of these diseases, the clinical physiologist has had great difficulty in elucidating underlying pathophysiologic mechanisms. No small hindrance to this progress has been the nature of the experimental animal himself, namely, man. Nowhere else in physiology does nondestructive observation place its strictest limitations. Available counterparts of spontaneously acquired human peripheral vascular disease are rare indeed in lower animals.

The History

The detection, clarification, and interpretation of a patient's own experience with his altered circulation (symptoms) may be just as important to the clinician and clinical physiologist as graphic recordings of circulatory parameters may be to the basic physiologist. For this reason, it seems worthwhile to discuss briefly the important aspects of this means of investigation. Where known, the physiologic mechanisms underlying these symptoms will be noted.

Several general aspects of the history are noteworthy. Age, sex, and race are important; e.g., arteriosclerosis is more common in the aged; Raynaud's disease is much more frequent in females; and Buerger's disease is extremely rare in Negroes and women (74). Because of their predisposing influences on subsequent vascular disease, a past history of polycythemia, frostbite, thrombophlebitis, diabetes mellitus, and many other disease states is important. Occupational factors should be explored, e.g., the predisposition to Raynaud's phenomenon seen in truck drivers and pneumatic hammer operators. Evaluation of environmental influences such as temperature, humidity, and body position is also important. The effects of drugs may be important, e.g., ergot, nicotine, and sympathicomimetic agents. Evaluation of emotional and other psychic factors are also of considerable importance.

More specific aspects of the history are as follows:

SYMPTOMS OF ARTERIAL DISEASE. Among the common symptoms associated with reduced arterial flow are

pain, tenderness, fatigue, paresthesia, altered sensations ranging from hyperesthesia to anesthesia, muscle cramps, and sensitivity to thermal change. Pain may be divided into three main groups: intermittent claudication, rest pain due to ischemic neuritis, and rest pain associated with trophic changes.

Intermittent claudication characteristically is pain produced by exercise and relieved with rest. It may appear in any muscle group and is usually due to organic arterial obstruction. It is related to the degree and/or rate of work (in the physiologic sense) over a certain time interval performed by a particular muscle group with its compromised circulation. Increasing the amount or rate of work produces a more rapid onset, a more severe degree of pain, or both. With reference to the lower extremities, clinicians attempt to quantitate claudication in terms of onset of pain after walking a certain distance (claudication distance) or after walking a certain period of time (claudication time) at a prescribed pace. This symptom usually starts as a sense of "fatigue" then progresses to a "cramping" pain. A major characteristic of claudication is relief with rest. When post-exercise relief does not ensue within 5 to 10 min, another cause for the pain is suspected.

"Vasospastic claudication" is a term used to describe a syndrome in which peripheral arterial pulsations are normally present at rest but disappear during exercise. The affected limb may then become pale and typical claudicatory distress occur (43). From clinical studies it is considered that the majority of this comparatively small group of patients have partial segmental occlusion of large arteries proximal to the site of claudication (36) and that superimposed arterial spasm is responsible for the ischemic manifestations on exercise.

The exact mechanism of intermittent claudication is not clear. That claudication is not due to muscle cramps has been repeatedly stressed, since the muscles are flaccid during the attack, and it is not due to vascular spasm of small vessels because the vessels to the muscles are dilated rather than constricted with exercise. Claudication indicates insufficient blood supply to the painful muscles to meet the increased metabolic needs of the muscle during exercise.

It appears that there are at least two basic requirements for the production of intermittent claudication: 1) oxygen lack and 2) muscular contraction in the presence of this anoxia (36). In this regard it should be noted that claudicatory pain has been produced in severely anemic patients with patent arteries (78) and that it has been produced by exercising normal

people while breathing air with low oxygen concentrations (40). It is noteworthy that intermittent claudication may be produced in a normal limb by exercise after artificial arrest of the blood supply. In the normal limb following circulatory arrest, the pain disappears quickly (usually within 3 sec) after restoration of the circulation, but if arrest is maintained the pain persists, presumably because the agents responsible for the pain are not inactivated in the presence of an inadequate circulation.

Lewis has shown that it is not oxygen lack itself that causes the claudicatory pain but rather the stimulation of sensory nerves by metabolic products of muscular activity which are ordinarily inactivated in the presence of an adequate blood supply with sufficient oxygenation. The mediating agent or agents from ischemic muscles to the pain-sensitive nerve endings has been called "factor P" or "pain factor." Apparently, it is a metabolic product of muscle and is rather stable, acid, and nonvolatile. Whether or not it is produced in increased quantities or is inadequately neutralized, inhibited, or dispersed in the face of ischemia is not known. Few definitive studies in this area are available. Among the more important are those of Lewis *et al.* (47, 51) and Katz *et al.* (37).

One observation that requires further exploration is the relief of deep pain by the application of ethyl chloride spray to the skin surface. Travell and associates (98) have reported pronounced amelioration of claudicatory distress by this means.

Ischemic neuritis is considered to be one of the mechanisms of rest pain in arterial disease. This type of pain, severe lancinating sensations and paresthesias, is characteristic of stimulation of neural elements. It is usually more troublesome at night when the patient is in bed. The pain of ischemic neuritis is found most frequently in vascular disturbances associated with diabetes mellitus and Buerger's disease.

The pathogenesis of the symptoms due to ischemic neuritis appears to be related to neural degeneration secondary to impairment of blood flow through the nutrient vessels of the nerves. In support of nerve degeneration is the associated reduction in vibratory sense perception and pinprick sensation.

Trophic changes may be responsible for pain occurring in the resting state. These painful sites are areas of ulceration and pre-ulceration which probably cause sensory nerve irritation through inflammation and ischemia. This type of pain is usually continuous in nature. It is more common in Buerger's disease

and in diabetic neuropathy probably because of the involvement of nerves in the inflammatory processes.

The pain associated with occlusive arterial disease is frequently accentuated by elevation and diminished by dependency of the involved part. Excessive local heat may be harmful and often increases the pain because of increased metabolism with restricted blood supply. Excessive cold may induce vascular spasm and also accentuate pain and tissue damage.

SYMPTOMS OF VENOUS DISEASE. Symptoms due to disease of the veins may include pain, muscle fatigue, muscle cramps, and paresthesias. Many of the symptoms of venous insufficiency (deep-vein thrombosis and obstruction, valvular incompetence, and varicose veins) are due to congestion and edema of the involved parts and therefore are affected by gravity. These symptoms are accentuated by dependency and diminished by elevation. Additional manifestations of venous disease and their pathogenesis will be found in subsequent sections.

MANIFESTATIONS OF CAPILLARY AND LYMPHATIC DISEASE. These diseases are discussed in other parts of this volume.

Physical Examination and Simple Clinical Tests of Vascular Function

In the sense that the basic physiologist must define the conditioning influences under which his laboratory experiments are conducted, so must the clinician define the conditions under which he makes his observations of disease processes. In this respect, in the examination of his patient for peripheral vascular disease, the clinician must make every attempt to control influencing variables in the environment. Under ideal conditions then, the changes observed during a "steady state" established by proper conditions for examination may be assumed to be due to the disease itself. To this end, standardization of the condition and technique of the examination is necessary.

The subject should rest supine in bed in a comfortable position with no constricting garments. The environmental temperature and humidity should be in a comfortable range. The parts should be dry and free from exposure to drafts. Blankets may be applied, if necessary, but when employed should cover all parts symmetrically. Local heat or cold should be avoided. Other influencing factors

such as recent use of tobacco, alcohol, or certain drugs should be controlled.

Because of the great number of variables in disease and because of the wide range of normal variation, the clinician must take advantage of "built-in" controls. To this end, he should carefully and continually examine and compare symmetrical parts of the body.

DETERMINATION OF THE ADEQUACY OF THE CUTANEOUS CIRCULATION. The presence and location of cutaneous ulcerations should be noted. In arterial disease these tend to be at the tips of the digits and over pressure areas, whereas in venous disease they tend to be located over the medial lower one-third of the leg. The skin should be examined for texture and consistency. The skin tends to be thin and shiny in arterial disease and thick and brawny in long-standing venous and lymphatic disease. Tissue swelling and edema tend to be absent in arterial disease, unless there has been considerable capillary injury, but they are frequent findings in venous and lymphatic insufficiency. Changes in the growth rate and appearance of the nails may be clues to impaired cutaneous circulation. The nails tend to be thickened, ridged, deformed, brittle, and pigmented. In vasospastic states there may be thinning of the proximal nail fold with merging into the cuticle (pterygium). Hair growth may be impaired. The degree of sweating is important. Absence of sweating may indicate

complete ischemic destruction of sympathetic nerve fibers or ischemic impairment of sweat gland function. Excessive sweating, in the absence of a demand of this function for thermal regulation, usually indicates increased sympathetic activity with intact nerves, frequently due to psychogenic disturbances. Other vascular manifestations of increased sympathetic activity with respect to temperature and color of the skin are usually present.

Temperature and color changes are of such importance in the evaluation of the cutaneous circulation that they demand special comment. The observations of Lewis (49) are still authoritative. Under standardized conditions, the amount of heat brought to the skin may be considered a gross reflection of the rate of local blood flow. It should be noted that the temperature of a part cannot decline more than 1 C to 2 C below room temperature and then only if the part is moist and the circulation completely arrested. The temperature rarely decreases below 20 C in a cool room and rarely exceeds 34 C in a warm room. Temperature differences of symmetric areas, similarly exposed, should arouse suspicion of circulatory disorder. When exposed to cold, the part with the better circulation will remain warm longer and on rewarming its temperature will increase faster.

Except for modification by skin pigments, the color of the skin is due mostly to blood in the venules of the subpapillary venous plexus and to a lesser

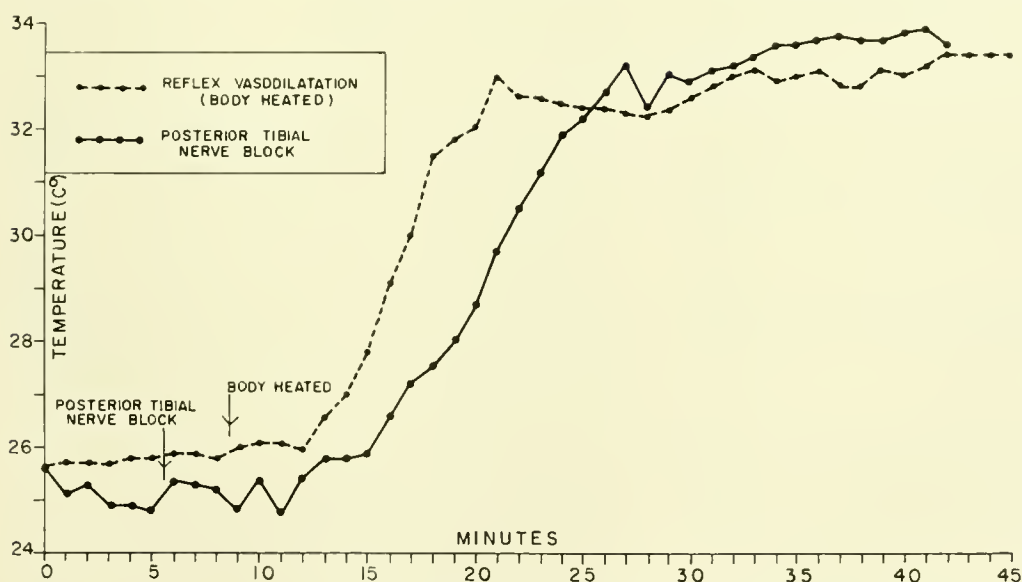


FIG. 1. Thermocouple recording of thermal change in the right big toe demonstrating the effects of reflex vasodilatation and posterior tibial nerve block.

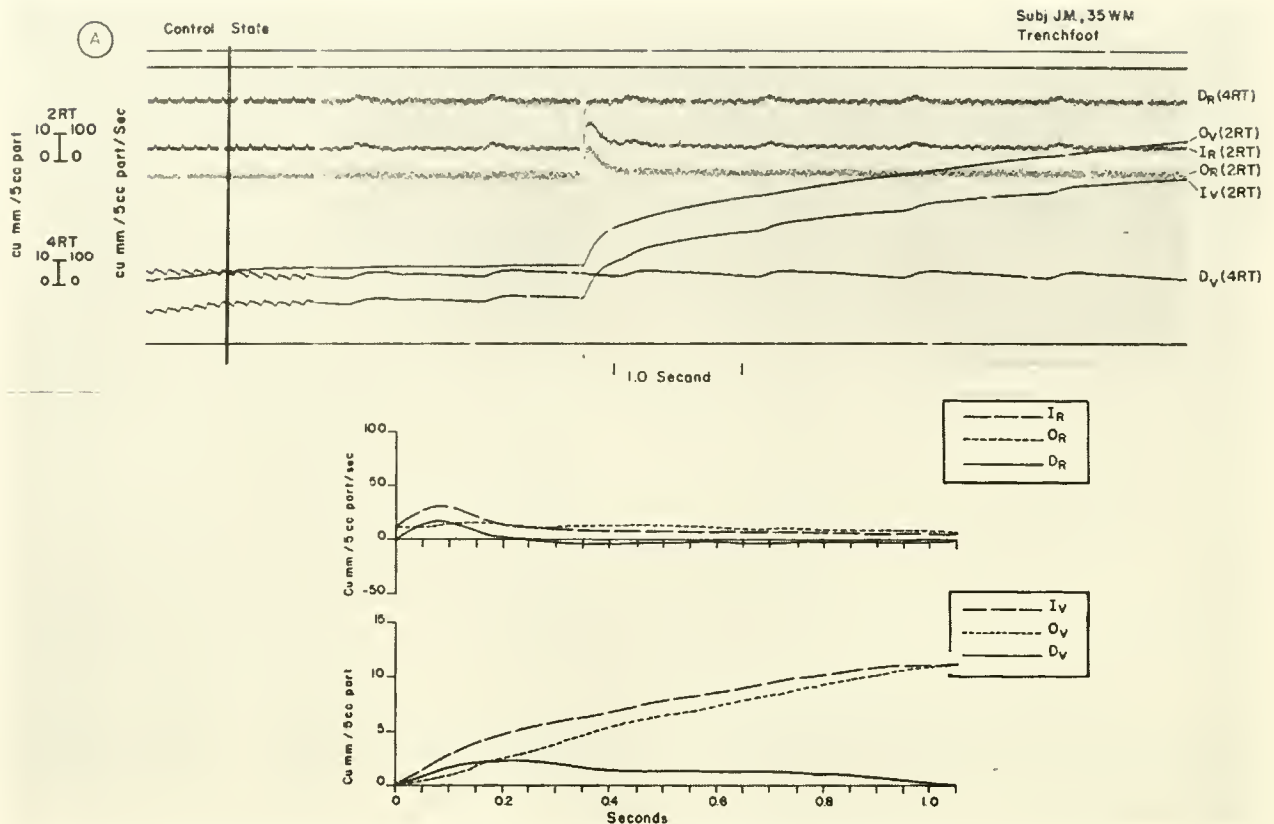


FIG. 2. Rheoplethysmographic recordings showing the simultaneous curves of volumes and rates of digital inflow, outflow, and the difference between inflow and outflow for the tip of the right second toe (2RT) during a single pulse cycle. *A* represents the curves for the subject resting supine in a comfortable environmental atmosphere, *B* following heating of the trunk, and *C* following procaine block of the posterior tibial nerve. I_V and I_R represent the time courses of the volume and rate, respectively, of inflow; O_V and O_R , volume and rate, respectively, of outflow; D_V and D_R difference between the volume and rate, respectively, of inflow and outflow. The reader should refer to the literature (10, 11) for a discussion of rheoplethysmography. See following pages for 2*B* and 2*C*.

degree to blood in the cutaneous capillaries. When the velocity of blood is slow, more oxygen is removed by the tissues, the concentration of reduced hemoglobin increases, and the color of the skin darkens and becomes bluer.

The integration of skin color and temperature has been aptly stated by Lewis (49). These characteristics, of considerable physiologic and clinical significance, are:

“Warm pale skin: This is a skin through which blood flows rapidly for many minutes. It is warm because flow is fast, pink because of the abundant supply of fully oxygenated blood, and pale because the skin is well nourished and minute vessel tone is therefore high.

“Warm deeply coloured red skin: Such skin has been irritated, by heat or otherwise, it is in a state of

inflammation, or it is skin in which arterial vasodilatation has recently been brought about through nervous channels or by means of drugs such as amyl nitrite.

“Cold pale cyanosed skin: This is skin to which the blood-flow is very slow or absent. If the tint of the cold skin is violaceous or if the skin is blanched, the circulation to it is absent and has been arrested in it for many minutes. Minor grades of cyanosis are, as previously stated, of much less significance.

“Cold deeply coloured cyanosed skin: This is skin in which the circulation is very slow, and in which blood-flow has been failing for a long time or in which there is a process of low-grade inflammation.

“Cold deeply coloured red skin: If skin is sufficiently cold, 10° C (50° F) or less, the blood will not part with its oxygen, but the minute vessels are damaged

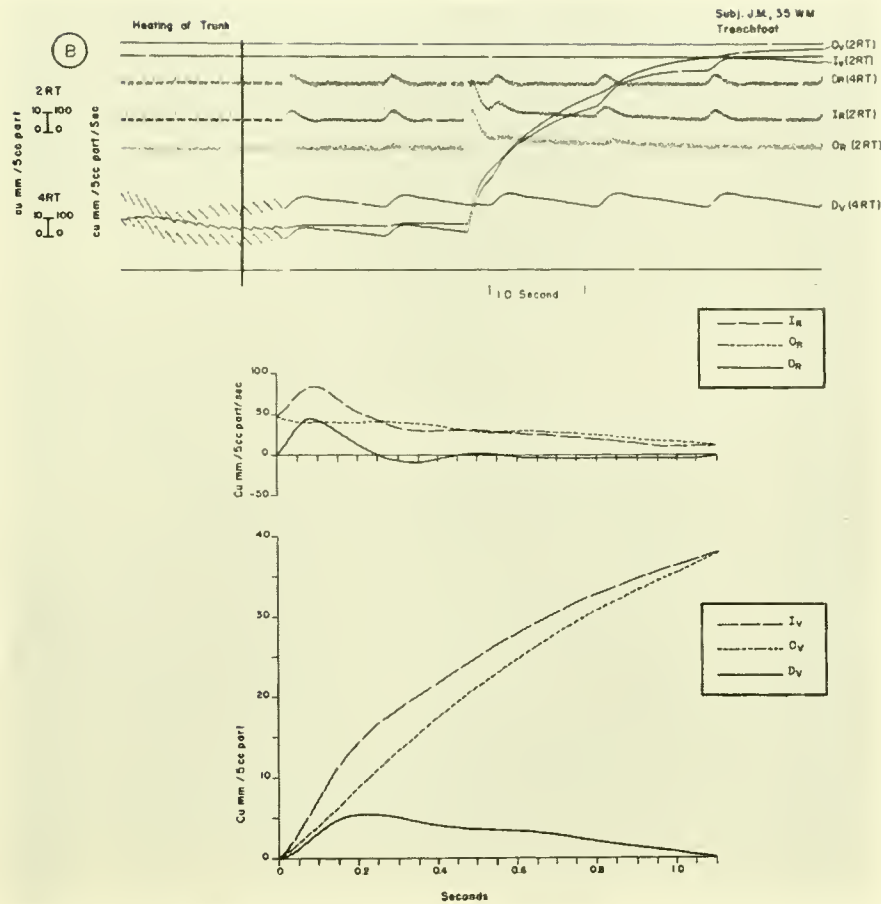


FIG. 2B

and dilate, and thus the skin becomes bright red in colour although the blood-flow through it may be small."

Some generalizations might be made from these correlations. If the temperature of a part is warm, there is a large volume flow; if it is cool, the volume flow is small. If the depth of skin color is pale, the cross-sectional area of the minute vessels is decreased; whereas if a deep color is present, the cross-sectional area is increased (vessels open). If the color is pink, the velocity of blood flow is fast and oxygen saturation high; if red, the velocity of flow is intermediate and the oxygen saturation is intermediate; if blue, the blood flow velocity is slow and the oxygen saturation low.

A crude estimation of the cutaneous circulatory status may be obtained from the *subpapillary venous plexus filling time*. Digital pressure on the skin for several seconds results in displacement of blood into adjacent and deeper lying areas. On sudden release of this pressure, the normal skin shows a change from the pallor to a normal color within 1 or 2 sec.

Gravitational effects on the cutaneous circulation may be employed in diagnosis and estimation of the state of the circulation by means of *elevation and dependency tests*. Here, the patient lies on his back with the legs flexed to 90 degrees at the hip. He holds this position for a certain length of time, usually 1 min. If he will tolerate it, the patient may be requested to flex and extend the ankle during this period. With impairment of the circulation, the skin assumes a white, waxy color during this maneuver. The patient is then instructed to sit on the edge of the examining table with his legs hanging dependent. Normally, gravity and reactive hyperemia cause a return of flushed color to the skin within a short interval of time, usually 15 sec. A delay in return of color is roughly proportional to the degree of circulatory insufficiency.

The *test of venous filling* may be performed simultaneously with the above gravitational test. The duration of time from the moment the patient sits until the superficial veins of the legs are filled is a gross indication of the circulatory status in the legs.

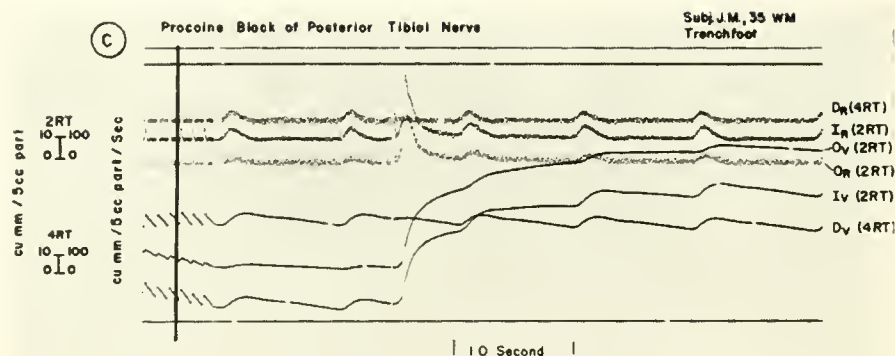
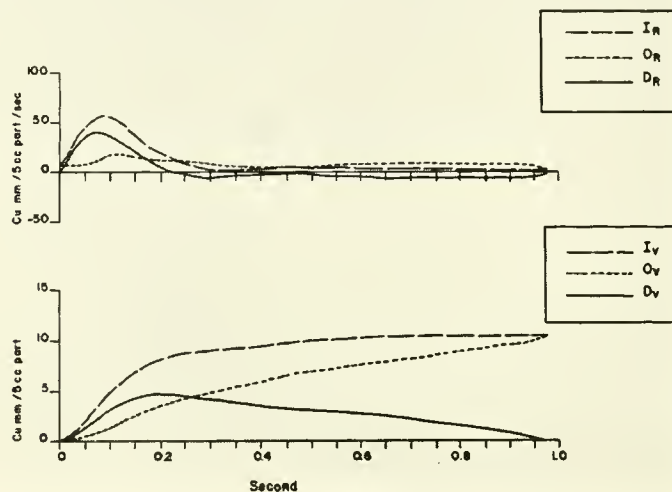


FIG. 2C



Normally, venous filling starts within 30 sec. For this maneuver to be valid as a test for arterial sufficiency, the veins must be relatively normal with competent valves. Venous valvular insufficiency is evidenced by abrupt venous filling.

Tests of vascular dilatability may be useful in the evaluation of the cutaneous circulation. *Reactive hyperemia* may be employed as such a test. The techniques and mechanisms for this reaction are discussed in detail elsewhere in this volume, but brief comments may be in order. As originally recommended (49, 77), the part to be tested is placed in water at 35 C to 40 C for 10 min then removed and raised above body level until pale. The purposes of this procedure are to ensure that vessels in spasm are relaxed and to empty the minute vessels of blood. A sphygmomanometer cuff is then placed about the part to be investigated and inflated to a pressure above systolic blood pressure. The limb is then returned to the water bath and maintained there for 5, 10, or even 15 min with the circulation arrested, if tolerated by the patient. The limb is then lifted out of the bath, dried, and its circulation released. In normal limbs, the reactive hyperemic flush reaches

the tips of the digits within 2 to 5 sec, becomes maximal in 15 sec, then quickly fades. When organic arterial occlusion is present, the flush spreads slowly, is patchy in distribution, and may be delayed up to a minute or so in reaching the tips of the fingers or toes. When disease is present and the onset is delayed, the flush lasts for much longer periods of time. More quantitative methods such as plethysmography or thermometry may be used to measure the reaction.

Vascular dilatability may be tested by *methods which decrease sympathetic tone*. For example, local nerve block (figs. 1, 2A, B, and C) or paravertebral and stellate sympathetic ganglionic nerve block may be employed with the responses of the circulation being measured graphically by temperature recordings, plethysmographic recordings, or other means. Vasospastic states due to sympathetic nervous activity become evident from the recordings. In normal subjects or in patients with functional vasospasm, interruption of sympathetic activity results in a rise in digital cutaneous temperature to approximately 32 to 35 C when the subject is at rest in a comfortable environment. For obvious reasons, the total rise above control levels is much greater in

patients with vasospasm than in normal subjects. In patients with obliterative arterial disease (organic), interruption of sympathetic innervation results in little change or only a moderate increase in digital cutaneous temperature, depending upon the degree of obstructive disease (usually only to about 28 C). A decline in cutaneous temperature from control levels following sympathetic inhibition indicates severe impairment of arterial circulation. This response may be due to a pre-existing lack or dysfunction of sympathetic innervation in the diseased area caused by ischemic degeneration of sympathetic nerves. Rigidity of the diseased blood vessel walls may be another factor. After induced sympathetic inhibition, blood is apparently shunted away to more healthy areas where the resulting decrease in vascular resistance would be proportionately greater. It should be remembered that tests dependent on inhibition of sympathetic innervation are of value clinically only in evaluation of the cutaneous circulation and are of little or no value in the investigation of the circulation to muscle.

The above tests, however, are of a special or somewhat complex nature. More simply, sympathetic inhibition may be induced by means of *reflex vasodilatation*. Reflex vasodilatation is produced by heating a part of the body other than that which is being tested. Application of a radiant heat tent over the trunk may be used with the temperatures maintained at approximately 50 to 60 C. Responses can be determined graphically by temperature or plethysmographic recordings (figs. 1, 2 A, B, and C) or other suitable means. Normally, the unheated tested limb may reach approximately 32 C when other parts of the body are warmed. Reflex vasodilatation is caused in large part by indirect sympathetic vasoconstrictor inhibition resulting from the action of warmed blood on central sympathetic temperature-regulating centers (30), but in part also by increased activity of the vasodilator fibers (100).

Another simple clinical procedure is the *histamine wheal test* (48, 93). The wheal formation of the triple response produced by intradermal injection of histamine is dependent upon the rate of local blood flow and capillary pressure. The rate at which the wheal forms is a rough indication of the status of cutaneous circulation. Briefly, the test is performed by slightly puncturing the skin several times with a sharp needle through a drop of 1:1000 solution of histamine acid phosphate. The subsequent reaction is then observed. It has been stated that if a wheal fails to appear within 3 to 5 min, ischemia of tissue

is severe; if a wheal does not develop at all, gangrene is imminent. Normally, the wheal develops in 3 min. The mechanisms of the triple response have been discussed in detail by Lewis (48, 49).

EVALUATION OF THE STATUS OF THE MAIN ARTERIES.

In the evaluation of the arterial circulation, one of the most important and informative procedures is a careful and methodical palpation of the main arteries, including all the major branches from the aorta to the digital ones. The abdominal portion of the aorta is readily palpated. The thoracic aorta may be palpated in advanced aneurysm formation. The digital arteries of normal people are usually palpable. When arterial spasm is present and the pulses are weak, sublingual administration of 0.4 mg of nitroglycerin (24) or the inhalation of amyl nitrite may release the vascular tone sufficiently to cause marked accentuation of arterial pulses. Obviously, arteries which have been totally and organically occluded will remain impalpable after this procedure.

For further information concerning functional states of the main arterial circulation, one often must employ more specialized procedures. With the foregoing diagnostic procedures, however, this is usually not necessary.

EVALUATION OF THE STATUS OF THE VENOUS SYSTEM.

The common signs of venous disease should be observed and evaluated. One of the most frequent is edema, which tends to be compressible or "pitting" in acute or subacute stages of formation but firm and less compressible when of long duration. Abnormally dilated and distended veins and venous varicosities are frequently present. Ulcers are common in long-standing venous insufficiency and tend to be located over the medial lower one-third of the leg. Also located in this area and frequently found in chronic disease is the so-called "stasis dermatitis," an atrophic, pigmented, chronic, low-grade inflammatory area of skin.

Several simple clinical tests are available for determining the competency of the venous valves and the patency of the deep veins. They are usually employed in the evaluation of varicose veins. Information pertaining to the clinical tests may be found in several publications (9, 54, 65, 67, 72, 79, 80, 99). The tests are well known and will not be repeated in detail here, but briefly some are as follows:

Brodie-Trendelenburg test (99). This test is designed to test the valvular competence of the saphenous and communicating venous system. It involves two

parts. In the first part the leg is elevated above the body, the veins are emptied, and a tourniquet is applied over the upper thigh tightly enough to occlude the superficial but not the deep veins. The patient then stands. If the superficial veins fill quickly (in less than 30 sec) then the valves of the deep to superficial communicating veins are incompetent. The second part of the test is similar except that the tourniquet is removed at the moment the patient stands. If the superficial veins fill immediately in a retrograde fashion, then the saphenous valve system is incompetent.

Perthes test (72). This test is designed to evaluate the competency of the saphenous and communicating valves and to test for deep vein patency. A tourniquet is applied to the thigh and the patient is asked to walk for 5 min. If the superficial veins collapse during this walk, there is an indication that the communicating valves are competent and the deep veins are patent. If no change is observed, the indication is that the communicating valves are incompetent. If the superficial veins become more prominent and pain is produced, there is an indication that the deep veins are obstructed and the communicating valves may be incompetent. This test utilizes the pumping effect of exercise on venous flow.

The Perthes test has been modified by Mahorner & Ochsner (54) to determine the location of the incompetent communicating veins. The modification involves the application of tourniquets to the upper thigh, above the knee and below the knee before walking. Observations are made on the veins below the tourniquet before and after each walking period, and if they collapse then the communicating valves below the tourniquet are competent.

The mechanisms involved in the above and similar tests should be obvious and will not be pursued further.

Determinations of venous pressure at rest and during exercise are of help not only in clinical evaluation but also in understanding the pathophysiology of many manifestations of venous insufficiency (valvular incompetence or venous obstruction) (9, 79). With significant venous obstruction or valvular incompetency, venous pressure in the leg fails to drop during walking as it does in the normal. Venous blood flow also fails to increase during walking. Thus, high venous pressure and sluggish venous flow persist during the normal daily activity of these patients. When venous obstruction is marked, venous pressure is even higher and the venous flow more sluggish than normal even in a recumbent position. The

increase in venous pressure is transmitted back to the venules and capillaries. Thus, the many factors of venous hypertension, stagnant flow, lowered blood oxygen tension, compression of tissue by dilated veins, delayed removal of waste products of metabolism, previous and present inflammatory reactions, edema, infection, and everyday trauma combine to produce the secondary manifestations of venous disease such as stasis dermatitis and dermal ulcers. In advanced stages, thickening of the walls, endothelial proliferation and degenerative changes may be found in arterioles as well as venules (3).

Edema formation secondary to venous obstruction or valvular incompetence is a topic of its own and will not be discussed here. Some aspects, however, are discussed in a subsequent section of this presentation.

EVALUATION OF THE STATUS OF CAPILLARY AND LYMPHATIC VESSELS. This evaluation is available in other portions of this volume.

Special Laboratory Procedures for Examining the Peripheral Circulation

Many of the specialized laboratory procedures for investigating the peripheral circulation are discussed elsewhere in this volume and are beyond the scope of the present discussion. Such methods include plethysmography, thermometry, calorimetry, intravascular and tissue pressure recordings, circulation times, blood-gas analyses, rate of radioisotopic clearance, arteriography, venography, lymphangiography, sweat studies, nailbed and scleral capillaroscopy, infrared photography, and oscillometry.

EFFECTS OF CIRCULATORY ARREST

Complete circulatory arrest lies at the farthest end of the spectrum from the normal state. Before progressing to disease, the effects of which may lie anywhere between these two extremes, it might be beneficial to review briefly the effects of complete arrest of the circulation. Much of these data are found in the publications of Lewis (48, 49).

With complete circulatory arrest the temperature of the part decreases to room temperature. The rate of decline is dependent upon environmental temperature, relative humidity, and air currents. The greater the mass of the part, the slower the decline. Pallor is the first change in color as the blood drains out of the minute vessels in the first 30 to 60 sec.

During the next few minutes the part becomes bluer and then definitely cyanotic.

Lewis (48) made interesting observations on the blood vessel reactions in the skin of the arm after obstruction of the brachial artery by a pneumatic cuff. After a few minutes of obstruction, red and white spots (Bier's spots) form in the cyanotic background of the surrounding skin. The red spots are due to leakage of blood into the area from collateral circulation through bone. The white spots are due to intense contraction of the vessels responsible for skin color, in particular, the subpapillary plexus of veins. Lewis excluded cold temperature and central and local nervous factors as primary causes of the white spots. They are formed in previously denervated areas. Through a careful series of experiments, Lewis showed that in cutaneous areas in which the circulation has been sufficiently reduced, vasoconstrictor as well as vasodilator substances are formed. The vasoconstrictor substances are released locally in the tissue spaces and are not derived from the blood. These substances act against potent vasodilator factors known to be released when the circulation is arrested. As noted by Lewis (48), these white spots enlarge and coalesce progressively as the skin is deprived of its circulation. He noted that at death the skin is initially congested but shortly afterward the white spots appear, spread, and coalesce until all but dependent parts of the skin are white or universally blanched. Responses comparable to Bier's spots have been described for organs other than the skin (86).

After its induction, if circulatory arrest to a limb continues, nervous changes develop, distally at first and then progress proximally up the extremity. Numbness occurs within 15 min and is followed by hypesthesia, first for pain and cold and last for warmth. With respect to the arm, motor changes occur in approximately 20 min, appearing first in the thenar eminence. Within 25 min motor paralysis is usually present in the thenar muscles and within 30 min in the interossei and extensor muscles of the wrist.

If the circulation is re-established within 30 to 60 min after its arrest, complete recovery usually occurs. When arrest is prolonged, severe changes occur. Within 6 to 12 hours there is muscle death and whealing and blistering of the skin. After circulatory arrest for 12 to 20 hours there is nerve destruction and after 24 to 48 hours, necrosis of the skin.

Recent studies (33, 88) of pathologic changes from acute ischemia in man have shown that after a few

hours of circulatory arrest a muscle contracture similar to rigor mortis develops. This does not progress inevitably to fibrotic (Volkmann's) contracture. Although the latter is a frequent occurrence, the initial contracture can be reversible. It was noted that the early changes can be accompanied by little or no obvious histologic alteration but somewhat paradoxically, restoration of the circulation at this stage often leads to sudden increase in the apparent severity of muscle damage. It is thought that the previous "normal" histology might be merely that of dead or dying muscle preserved in a cool environment and that subsequent circulation of warm blood results in the demonstrable vascular engorgement, swelling, exudation, and focal hemorrhage with release of myoglobin and consequent muscle pallor. Depending on severity and duration, the involved muscle can recover completely or suffer any degree of damage (with subsequent fibrotic contracture) up to complete necrosis. It was observed that skin is more resistant to ischemic damage than is muscle, and muscle can be irreversibly damaged even though the skin remains viable. From these studies it was difficult to place a definite length of time for circulatory arrest to produce irreversible change, but a gross estimate was 12 hours or less.

With respect to the clinical implications of the above studies in the management of acute arterial occlusion by thrombo-embolectomy, it is worthwhile noting that blood in an artery distal to an occlusion usually remains fluid for 8 to 12 hours (4). Afterward the tendency to thrombosis and progressive distal arterial occlusion increases rapidly.

CLASSIFICATION OF PERIPHERAL VASCULAR DISEASE

The classification of peripheral vascular disease included in the APPENDIX to this chapter although not all-inclusive is fairly complete. It represents a modification of the classification suggested by the Criteria Committee of the New York Heart Association (15). It serves to emphasize the enormous problem and types of peripheral vascular disease. Each entity in the classification represents a separate complex experiment in nature. An adequate discussion of each would be impossible. For more elaborate descriptions of these diseases and for references, the reader may consult monographs on the subject (1, 3, 87, 104) and two recent symposia on peripheral vascular diseases (95, 96). The diseases selected for discussion here are the more common ones as well

as those primarily oriented best from the standpoint of discussion of mechanisms in peripheral vascular disease. Particular emphasis is placed on vasoconstrictor and vasodilator disease states.

MECHANISMS IN PERIPHERAL VASCULAR DISEASE

Vasoconstrictor Disease Syndromes

RAYNAUD'S SYNDROME OR PHENOMENON. This syndrome or phenomenon had been known for years before the time of Raynaud. Ragnetta, Huguier, Virchow, Zambaco and others commented on the syndrome, but Raynaud's thesis published in 1862 (84) first brought wide attention to the syndrome as a distinct entity. Since that time Lewis' work has been outstanding (46, 48, 49).

For purposes of classification and diagnosis one may refer to *a*) primary (idiopathic) Raynaud's syndrome or phenomenon, and *b*) secondary Raynaud's syndrome or phenomenon. When Raynaud's syndrome occurs as a primary manifestation and without any obvious underlying or predisposing cause, it is termed "primary." When the syndrome occurs as a result of, or in association with, some other disease which is known to be of significance in predisposition to or production of the syndrome, it is termed "secondary." Obviously, the classification of the secondary type is somewhat crude, since it is based upon empiric observation of an association of the syndrome with some other disease process with a frequency not expected in otherwise normal people. Certainly the primary syndrome must be secondary to its cause. Nevertheless, for diagnostic, prognostic, and therapeutic reasons, this classification is helpful. Raynaud's disease is the term applied when the typical phenomena have been present for 2 years without detection of any obvious cause. Although this terminology is arbitrary, it is clinically valid since most diseases in which Raynaud's syndrome is a secondary manifestation are usually diagnosed within a 2-year period (22).

Raynaud's syndrome characteristically consists of transient episodes of digital pallor, cyanosis, and erythema. The typical progression would be from pallor, to cyanosis, to erythema, but this is not always true. Erythema is not invariably noted and its presence is not a requirement for diagnosis. Although a pale blue-gray reaction usually precedes the stage of pallor (or cyanosis when pallor is absent), it frequently escapes notice. In order to diagnose

Raynaud's syndrome confidently there should be at least intermittent attacks or crises of either digital pallor (syncope) or digital cyanosis. Both may be present and either or both may be associated with subsequent erythema.

Primary Raynaud's phenomenon and Raynaud's disease. Raynaud's disease usually, but not invariably, appears before the age of forty and is much more frequent in females. Typically the vasomotor episodes are precipitated by exposure to cold and occasionally by emotional stress. In diagnosis, blanching can often be produced by submerging the hands or feet in water at an optimum temperature (49) of approximately 15 C (range, 12 to 18 C) for 10 to 15 min, but failure to produce the characteristic manifestations of the attack does not exclude the diagnosis (1, 49, 60). However, failure to produce blanching by this means plus additional preliminary or simultaneous general body cooling (e.g., a cold shower) is reliable evidence that Raynaud's syndrome does not exist. Water of icy coldness tends to produce a red reaction even in patients with Raynaud's syndrome. It is important to differentiate Raynaud's phenomenon from cold allergy which produces an erythematous pruritic edema but not true blanching (60).

The vascular reactions and color changes of Raynaud's syndrome tend to occur segmentally and bilaterally in the digits, generally terminating at the interphalangeal or metacarpophalangeal articulations. Although there is a distinct tendency for the syndrome to occur bilaterally and symmetrically some asymmetry in degree of involvement of either hand is not uncommon. Involvement of an extremity characteristically does not extend proximal to the metacarpo(tarso)phalangeal joint. The feet may be involved, but the hands are involved much more frequently. Involvement of other parts of the body is occasionally seen, especially such acral parts as the ear lobes, cheeks, tongue, and the tip of the nose.

The localization of the vascular lesions to the hands and feet is of interest. When only a single phalanx is involved, it is the distal one; when two phalanges are involved, they are the distal two. All three phalanges of a digit or several digits of either hand may be involved. In a single digit the direction of progression of changes during an attack is from distal to proximal. The second or fifth or both digits are involved most often. When only the very tip of the distal phalanx is involved, this suggests changes in vessels smaller than the digital arteries. Localization of Raynaud's reaction, which rarely occurs in parts of the body other than the digits, is apparently

due to vascular changes in the reticular-perpendicular arterioles in the skin of these sites.

Manifestations other than the typical color changes may be present. During the pallid or cyanotic crises, digital paresthesias may be present. During the erythematous phase there may be increased warmth and a painful throbbing sensation in the affected digits. After long-standing or severe disease, ulceration, necrosis, edema, or subungual and paronychia infection may develop (fig. 3). Ulcers usually occur on the digital tips and these may be quite painful. When they heal, they typically leave small pitted "stellate" scars. Another change that occasionally develops in long-standing or severe disease is sclerodactylia. The digits show a tight, tough, inelastic, fibrotic, and contracted skin with areas of hyperpigmentation and hypopigmentation. This change must be differentiated from *a*) acrosclerosis, in which similar changes involve not only the digits but also the face and neck; and *b*) scleroderma, in which fibrotic changes are generalized, even involving multiple visceral organ systems.

Practically nothing is known of the earliest pathologic changes in Raynaud's disease. This is due in large part to the lack of biopsy specimens obtained during the early stages of the disease. Physicians and investigators have been reluctant to obtain biopsies in these patients. Simple digital biopsy methods and other means are now available whereby early changes may be observed, both by light and electron microscopy not only in Raynaud's syndrome but also in other peripheral vascular disorders (32, 73, 75). Based on light microscopy, it has been assumed that pathologic changes are absent in early Raynaud's disease. More sensitive methods, such as electron microscopy, may alter this impression. In



FIG. 3. Primary Raynaud's disease with trophic changes and early sclerodactylia.

the later stages of the disease, intimal thickening of the digital arteries is almost always present. In still more advanced stages the internal elastic membranes split and there is endarteritis obliterans with thrombi in various stages of recanalization. The latter changes are particularly frequent in association with ulceration.

Briefly, and in general, the mechanisms for Raynaud's phenomenon are as follows: Pallor is due to digital arterial constrictive crises to the point of, or almost to the point of, complete occlusion with resultant absence or near absence of digital arterial blood flow. Capillary pressure drops to about 5 to 10 mm Hg (60). Cyanosis occurs when digital arterial constrictive crises are slightly less severe, allowing some blood to flow. In this situation the slow rate of flow fosters an increased dissociation of oxygen from hemoglobin with resulting local cyanosis. During the recovery phase from the vasoconstriction, erythema frequently ensues due to reactive hyperemia. These physiologic changes are fairly well accepted as the vascular reactions responsible for the typical digital color changes. Controversy still exists, however, regarding the location and nature of the underlying factors responsible for initiating vascular reactions. Raynaud felt that the primary factor was a derangement of the nervous system (84). Adson & Brown (2) also considered the basic fault in early Raynaud's disease to exist entirely in the vasomotor nerves, since complete relief of Raynaud's reaction occurred in many patients following sympathetic ganglionectomy.

Lewis (48, 49), however, maintained that the basic fault is in the digital arteries themselves and that the defect consists of an abnormal sensitivity of the arteries to direct stimuli, particularly to cold. In Lewis' own words (49), "The central fact is transient loss of circulation to the digits occurring on exposure to cold. I have shown that this spasmodic loss of circulation is due to closure of the digital arteries, and that, irrespective of its nature, the fault lies in these vessels; the closure does not involve arteries of much larger size, neither does it include arterioles or veins. But since the attack is induced by exposure to cold, to which all vessels normally respond, a general reduction of their size happens. In most of the vessels the degree of closure can be regarded as no more than normal. In the small arteries only is the response to cold manifestly abnormal; these are in a state rendering them particularly liable to shut on direct exposure to cold. In sensitive cases, the blood-flow to a single finger can be arrested

at will by cooling this finger alone, or even by cooling a short stretch of it; for the digital arteries in their whole length possess this liability to closure. The state of closure once established can be released by warming the hands; and this can also be affected in the arteries of separate fingers, or even in the arteries at the base of a finger, by warming the finger or its base separately.

"It has been indicated already that, when a normal subject is exposed to cold, arteries like the digital narrow under two influences; they constrict as a direct reaction to cold, and because vasomotor nervous tone increases. These same two factors operate in the fingers of the cases we are discussing, under conditions of general cooling. But, because in these cases there is an abnormality, the vessels do what they will not do in normal subjects, they close to obliteration. The evidence proves that the abnormal element is local, and not, as formerly thought, in the response of the nervous system. Thus, if vasomotor tone is deliberately reduced by warming the subject's body, immersion of the hand of a susceptible subject in cold water will still induce the attack; but if the hand is kept warm, an increase of vasomotor tone, induced by cooling the body, will not provoke the attack. Again, if the circulation to the fingers of such a patient has become arrested by general exposure to cold, local destruction of vasomotor tone by nerve anaesthetisation does not bring instant release of blood-flow, which would happen inevitably if vasomotor tone were alone responsible: it brings delayed release, or the release fails. Likewise, as experience has shown, destruction of the sympathetic nerve supply to the limb by surgical intervention does not cure the malady: for it frequently happens that patients so treated continue subsequently to display attacks on exposure to cold; and after sympathectomy the local susceptibility can always be demonstrated by special tests in sensitive cases and this is so even when the sympathectomy is preganglionic. The local abnormality is the reason for this, for it remains unchanged.

"Although the facts show that the fault is not in the nervous system, that is not to say that the nervous system plays no part in the attacks. If under the direct influence of cold the arterial channels of a hand become unusually narrowed, but not quite obliterated, then subsequent cooling of the trunk, or an emotional disturbance, or a painful stimulus, by normally increasing vasomotor tone, will cause the vessels to close completely and thus determine an attack. It is this kind of event that has been

misinterpreted in the past, and has given support to the wrong idea that the vasomotor nervous system is primarily at fault. Further it will be apparent that anything reducing or abolishing vasomotor tone will on occasion bring an attack to an end, and continuing as an influence will tend to prevent the recurrence of attacks. This is the basis upon which the modern treatment by sympathectomy rests; its successful results are due, not to interference with the passage of abnormal nervous impulses, but to the destruction of normal vasomotor tone."

Lewis emphasized that if one finger of a subject with the disease is immersed in cold water, the attack is frequently confined to this finger. He felt that such a sharply localized response could not be explained on the basis of a nervous reflex.

More recent publications (8, 52, 62) presented evidence in support of Lewis' theory of a "local fault" in the blood vessels. By plethysmography and thermometry it was demonstrated that patients with Raynaud's phenomenon have an increased sensitivity to cold as compared to normal subjects and that this state persists even after successful sympathetic denervation. These studies were not meant to imply that sympathectomy is of no benefit to the patients. When the patient's peripheral vessels are maximally dilated by the procedure and heated by the warm blood flowing through them, a decrease of the vessel temperature to the critical level is not as easily produced. Further, cooling of the vessels by vasoconstriction can no longer be induced reflexly from emotional disturbances, pain, or body chilling.

Whether or not other vessels besides the digital arteries participate actively in the Raynaud's reaction has been debated. Naide & Sayen (66) considered that arterial spasm alone cannot explain the entire clinical picture. They presented evidence, though not conclusive, that spasm of the digital veins, as well as the digital arteries, exists. It was based largely on observations that in some patients with Raynaud's disease the digits began to appear puffed and cyanotic before blanching occurred. The authors considered this to indicate venoconstriction prior to arterial constriction.

Capillarioscopy has been of value in detecting vascular change in the various reactions of Raynaud's disease (3, 18). During the stage of pallor, no blood enters the capillaries of the involved digits. During the stage of cyanosis, more than the usual number of capillaries are engorged with blood, and many are greatly dilated. They are filled with stagnant blood. Venules may also be dilated during this stage,

and there may be reflux of blood from the venules into the capillaries. The transient cyanotic reaction in Raynaud's disease is similar to the more nearly permanent cyanosis of acrocyanosis in which secondary dilatation of capillaries and venules results from arteriolar spasm (3). During the erythematous phase, capillary pulsations may be detected. It should be recalled that in Raynaud's disease the vessels supplying the hand (radial and ulnar) are normal and continue to pulsate normally during the crises.

The main controversy remains concerning the initial basic defect in Raynaud's disease, that is, whether or not it is in the nervous system or in the vessel wall itself. Certainly in advanced stages the easily demonstrable intimal thickening and thrombosis of the vessels contribute significantly in reducing blood flow. It is probable that a vicious cycle is induced whereby repeated vasospastic attacks cause increasing injury and structural changes in the digital vessels which then become more vulnerable to vasospastic influences (60). Nevertheless, the important pathogenic factors in the early stages are still not known and very little recent definitive research in this area has been reported.

Some recent studies, however, are of interest. Using chromatography and biologic assay, Peacock (70) determined the concentrations of epinephrine and norepinephrine in the peripheral venous blood collected at the wrist in a group of normal subjects and in a group of patients with primary Raynaud's disease. He found that under warm resting environmental conditions, the Raynaud's patients showed a significantly higher blood level of these amines than did the normal subjects. Following sympathetic nervous stimulation by cold, the patients with Raynaud's disease had an increase primarily of the norepinephrine fraction. This increase varied directly with the clinical severity of the disease. Peacock considered the high concentrations of these amines to be due to an abnormality in metabolism of these substances. It was noted that in Raynaud's disease the average digital cutaneous temperature in a room temperature of $20\text{ }^{\circ}\text{C} \pm 5$ was $22.3\text{ }^{\circ}\text{C}$ compared with $30.2\text{ }^{\circ}\text{C}$ for the normal subjects. Similar differences had been reported for environmental temperatures as high as $25\text{ }^{\circ}\text{C}$. It was reasoned that over this range of temperature, due to precooling of blood by counter-current flow mechanisms, the intraluminal temperature of the blood in the digital arteries of patients with Raynaud's disease was probably considerably lower than that seen in normal control subjects. Thus, it was concluded that the lower temperature inhibited

enzyme systems which inactivate epinephrine and norepinephrine and that this was responsible for the higher concentrations of the vasoconstrictor substances and the intense peripheral vasoconstriction. In this respect monoamine oxidase activity of digital arteries of two patients with Raynaud's disease was absent, whereas that of two normal subjects was found to be $552\text{ }\mu\text{l O}_2$ per g per hour.

These studies are interesting but many questions remain unanswered. For example, the effect of reduced blood flow *per se* on the concentrations of amines in the venous blood draining these areas is not known. Concentrations may be greater but the total amount may be the same or less. Further, with respect to these amines, the relative contributions of *a*) increased amount in stores, *b*) increased release from stores, *c*) decreased destruction, *d*) impeded physical removal, and *e*) increased vascular sensitivity are also unknown. Furthermore, the role played by reduced formation of vasodilator metabolites from cooled tissues [as proposed by Freeman (27, 28) and later by Perkins *et al.* (71)] in the pathophysiology of Raynaud's disease needs investigation.

Recently, Mendlowitz & Naftchi (61) have reported observations on digital blood pressure (Gaertner capsule) and digital blood flow (calorimetry) in 20 patients with primary or idiopathic Raynaud's disease. The patients were studied at rest, under standardized conditions, before and after vasodilatation (reflex vasodilatation) and after vasoconstriction produced by infused *l*-norepinephrine. After appropriate calculations, they noted that their patients fell into two groups: 1) those with digital vascular obstruction and normal vasomotor tone, and 2) those without obstruction but with heightened vasomotor tone. Neither group showed increased sensitivity to norepinephrine. Thus, the authors suggested that the digital vasospastic crises in Raynaud's disease could be produced either by vascular obstruction acted upon by normal vasomotor tone, or by heightened vasomotor tone produced by increased sympathetic neural discharge acting on otherwise normal vessels.

The relationship of these latter findings to those of Lewis (49) and the more recent ones of Peacock (70) is not clear. With reference to the grouping offered by Mendlowitz and Naftchi, it is possible, but not proved, that Lewis was studying patients in the group with vascular obstruction and normal vasomotor tone, whereas Peacock was studying patients in the group without obstruction but with

heightened tone. Thus, there are many problems in Raynaud's disease which await clarification.

Secondary Raynaud's syndrome or phenomenon. A glance at the classification of peripheral vascular disease (see APPENDIX to this chapter) reveals that Raynaud's phenomenon occurs as a secondary manifestation in a number of disease states. The proposed mechanisms involved in these entities are complex and a description of these is beyond the scope of the present discussion. Further, little definitive work has been done to determine the true physiologic mechanisms responsible for the relationship between these diseases and secondary Raynaud's syndrome. In general, what has been said regarding primary Raynaud's phenomenon may be applied to the secondary phenomenon. There are a few known differences. In the secondary state the associated manifestations of the primary predisposing disease are evident. With obliterative arteriosclerotic endarteritis, Buerger's disease, or other obliterative arterial states, the degree of gangrene associated with secondary Raynaud's phenomenon may be considerably more than in primary Raynaud's because of the underlying obliterative disease. In the secondary state, exposure to cold or emotional stress may or may not precipitate Raynaud's phenomenon. Lastly, secondary Raynaud's phenomenon is frequently neither bilateral nor symmetrical.

It is often suggested that the observation of Raynaud's phenomenon occurring in diseases of the nervous system refutes Lewis' idea of a local arterial defect and that primary Raynaud's disease is a disease of neural origin. Even though this problem is unsettled, it must be remembered that differences between primary and secondary Raynaud's phenomenon do exist. Further, Raynaud's phenomenon from neural disease still might be due to excessive sympathetic nervous activity in the presence of "normal" digital vessels, whereas primary Raynaud's disease might be due to a local vessel defect in the presence of normal sympathetic nerve activity.

ACROCYANOSIS. Acrocyanosis is a disorder characterized by a persistent cyanotic rubor to the skin of the hands and feet and other acral portions of the body associated with a reduced skin temperature. The term "acrocyanosis" was first applied by Crocq (16) in 1896, and Cassirer's description (12) in 1912 helped clarify this disorder as a distinct clinical entity. Lewis & Landis (50) initiated basic investigations into the pathophysiology of this disease, but only a few con-

tributions to its mechanisms have been available since.

The etiology of acrocyanosis is unknown. In his large series of several hundred patients, Stern (94) was unable to detect any constant precursor or accompaniment of the disorder other than cold, with frequent moderate cooling of affected parts, and possibly inactivity, the latter because of the occurrence in lethargic types of mental disorders. It is much more frequent in females and usually present in young or middle-aged individuals. There is frequently a family history of the disorder. It has been described as being rare in the general population but rather common among the inmates of mental institutions.

The patient usually visits the doctor for cosmetic reasons, complaining of almost constant coldness and bluish discoloration of the fingers, hands, nose, cheeks, chin, and pinna of several years' duration (fig. 4). The toes and feet may be involved, but usually to a lesser degree than the hands. The changes, though present during the summer, are usually more marked in the winter. The affected parts are usually deeply cyanotic when cold, and bright red when they are very cold or when they are warm. Frequently they present a mixture of the two colors, red and bluish-purple. The deep reddish color (as opposed to cyanosis) produced by a very cold temperature (less than 10 C) is due to arteriolar injury and dilatation



FIG. 4. Acrocyanosis. [Reprinted with the permission of H. K. Lewis & Company, Ltd., London (94).]

and inhibition of oxygen dissociation from hemoglobin.

The palms are often sweaty. The hands are usually much colder than normal during exposure to a comfortable temperature but warm readily in a hot room. The disease varies considerably in degree from very mild to severe.

In the past, acrocyanosis has been confused with Raynaud's disease but many differentiating features are apparent. In acrocyanosis the color changes are persistent rather than episodic. The changes are not limited to the digits but include the entire hand and foot, though they rarely extend proximally to the wrist or ankle areas. There may be associated livedo reticularis or pernio involving more proximal areas of the extremities. There are usually no episodes of blanching, sclerodactylia does not develop, and areas of ulceration and gangrene are generally absent. Swelling however may occur, particularly in cold weather, and occasionally localized areas may become tender or painful. Although spontaneous ulceration is extremely rare, traumatic lesions in affected areas may become infected and heal slowly. Palmar clamminess is a well-known feature of acrocyanosis and differs from the dry skin of Raynaud's disease which appears when the local circulation ceases (94). In true acrocyanosis, examination of peripheral arteries reveals no evidence of occlusive organic arterial disease. The dependent cyanosis frequently present in the feet of patients with occlusive arterial disease should not be classified as acrocyanosis.

As in early Raynaud's disease, very little is known of the pathology of acrocyanosis. Stern (94) studied sections from the dorsal skin of the hands and feet of 12 patients with acrocyanosis. It was found that the medial coats of nearly all arterioles were thickened. Local edema and dermal fibrosis frequently were present in association with considerable dilatation of the superficial capillaries with formation of new capillaries. Others have described distention of the venules and venous limb of the capillaries and have noted large capillary loops occurring in increased numbers in the nail bed (3, 6, 41). In fact, this tendency to dilatation of the venous side of the circulation with a marked decrease in venomotor tone is a characteristic feature of acrocyanosis.

Little work is available on the vascular mechanisms responsible for acrocyanosis. Most evidence points to excessive arteriolar constriction which occurs at ordinary environmental temperatures and which is increased by cooling. The arteriovenous anastomoses are also probably constricted (60). This constriction

is followed by secondary dilatation of capillaries and venules with stasis in the minute vessels of this skin. There is loss of capillary and venular tone (6, 60), thought to be due in large part to anoxia. Stasis allows increased formation of reduced hemoglobin and the associated deep cyanosis, the blue color being due to increased amounts of reduced hemoglobin and the deep character of the color being due to the engorgement of the vessels. That venous obstruction is not a significant factor has been pointed out by Lewis & Landis (50) from the simple observation that cyanosis is abolished by venous drainage produced by elevation of the involved part. The color of the cyanosed skin is not uniform, since it frequently contains bright red areas (cinnabar red spots) (94) and occasionally changing reticular areas of pink color due probably to temporary relatively normal rate of blood through the perpendicular-arteriole reticular-capillary network (22). It has been noted that acrocyanosis is less pronounced in the presence of hypertension, since the latter tends to produce more normal circulation in spite of the dermal arteriolar spasm (60).

In acrocyanosis, the white spot produced by external pressure on the cyanosed part disappears spontaneously in a very characteristic fashion (94). The color returns from the periphery and not from below as in normal skin.

Comments by Lewis concerning the mechanism of acrocyanosis are worth quoting (49):

"The minute vessels of the skin are very dilated, as is evident equally from macroscopic and microscopic examination. But the temperature of the hands and other tests show the blood-flow to the skin to be reduced greatly. The veins though contracted by cold are not occluded. The pulses in the main arteries are normal. The constriction is in the small arteries or arterioles of the skin. If the hand at the time is cyanosed and a small part of it is warmed, the latter soon becomes sharply defined as a bright red area; similarly if a little histamine (1 in 3000) is pricked into the skin, the skin reddens locally and its temperature rises. This is in contrast to the cyanosed skin in the attack of Raynaud's disease, where the obstruction lies in the main digital arteries, and in which reddening of the skin does not occur in similar tests, but only after these arteries open. In acrocyanosis all the arteries and arterioles are capable of opening widely; gross structural impediment is not present in any of their channels."

Again, as in Raynaud's disease, whether the basic underlying disorder lies in the sympathetic nervous system or in the vessels themselves is unknown. As

FIG. 5. Livedo reticularis (lower portions of both legs of patient lying supine).



Lewis (49) noted, however, the arterioles in affected areas are in an unusually high state of tone. He was of the opinion that this is due to a fault in the vessels themselves, since anesthetizing the appropriate nerves does not result in prompt relief of the arteriolar spasm, as it would if the mechanism were neural in origin. In contrast, observations by Day & Klingman (17) were interpreted as showing predominant sympathetic nervous influences as the basic mechanism. They noted that during sleep the cyanosis and cold skin are relieved and replaced by warm, red skin.

No definitive studies are available in acrocyanosis concerning the significance of tissue catecholamines and other vasoactive substances. Nevertheless, comments made above on Raynaud's disease in this regard might be equally applicable here.

Since the course of acrocyanosis is relatively benign and complications are few, sympathectomy has rarely been indicated in its treatment. Because of this, controlled studies on the effects of sympathectomy are unavailable. In severe cases, however, sympathectomy may be of value, especially when there is an associated hyperhidrosis. The usual protection from cold or sudden and marked decline in temperature is indicated. The patient should keep warm and dry with serious attention being given to his general state of health.

LIVIDO RETICULARIS. Livedo reticularis is characterized by a prominent mottled, reticular, or blotchy reddish-blue discoloration of the skin of the extremities (fig. 5). Between the reticular discolorations, the skin presents a more normal but pale appearance.

Kaposi was probably the first to use the term "livedo reticularis" (3). The etiology of this disease

is unknown. That it may represent a congenital anomaly of blood vessels has been suggested by some (85, 103). Some are of the opinion that there is some inherent vascular instability in the background of most patients (3). In one series, 30 per cent of the patients had associated hypertension and 50 per cent demonstrated marked nervous instability (3, 5). Livedo reticularis is more frequent in females and usually appears before the age of 40.

The disorder usually involves the skin of the legs and feet in greatest severity, but it frequently also involves the arms and hands. Occasionally, the thighs and the lower part of the trunk may be affected. There is a distinct tendency for the disease to occur bilaterally and symmetrically.

The characteristic color changes are usually intensified on exposure to cold and tend to be alleviated on exposure to a warm environment. Patients may complain of numbness, tingling, coldness, or aching over the involved legs and feet. Ulcerations in livedo reticularis are not frequent but they do occur. Ulcers usually begin as an intensification of change in areas of marked cyanosis, usually over the medial lower one-third of the leg. These lesions may be very painful and slow to heal. Ulcers in some patients seem to be precipitated by cold weather, whereas in others warm weather seems to be important in their formation (23).

The pathophysiology and clinical findings in livedo reticularis have been the subject of several reports (20, 48, 85, 103); the most recent one of significance is by Feldaker *et al.* (23). The latter authors, following the suggestion of Williams & Goodman (103), preferred to classify livedo reticularis into three groups: 1) cutis marmorata, 2) idiopathic

livedo reticularis (primary livedo reticularis), and 3) symptomatic livedo reticularis (secondary livedo reticularis).

Cutis marmorata refers to a state characterized by transient reticular discoloration producing a marble (hence the term "marmorata") pattern to the skin which appears on exposure to cold but, unlike the other types of livedo, it is not permanent and disappears with warmth. It is considered that in this state there is no organic pathologic alteration in the peripheral circulation but rather that the disturbance is a vasomotor phenomenon. It has been noted to be frequent in infants and young girls and may disappear as they grow older.

In idiopathic livedo reticularis (primary livedo reticularis) the reticular discoloration is relatively permanent and persists to some degree regardless of temperature changes. As noted before, however, the degree of discoloration is accentuated by exposure to cold. There may be minimal to no organic changes in the vessels except increased number and dilatation of capillaries in the livid areas. Feldaker *et al.* (23) also noted in these areas varying degrees of endarteritis and endophlebitis of the smaller vessels. At times there is occlusion, periarteritis and periphlebitis and occasionally, thickening of the walls of arterioles in the dermis and subcutaneous tissue.

Symptomatic livedo reticularis (secondary livedo reticularis) is the form of the disorder associated with or secondary to other dermal, vascular, or systemic diseases. These have been outlined in the accompanying classification of peripheral vascular diseases (see APPENDIX to this chapter).

The large arteries such as the dorsalis pedis, posterior tibial, and popliteal are not involved by occlusive disease and likewise venous insufficiency is not a factor in livedo reticularis. Digital blood flow after interruption of sympathetic nerve supply is usually normal (60). Feldaker *et al.* (23) have recently summarized the probable pathophysiology of this disease. The perpendicular arterioles, supplying the skin from below, and the central zone capillary arborizations have a slightly greater tone and faster linear rate of blood flow than the peripheral capillaries. Either because of organic change (as described earlier) or vasospasm of arteries and arterioles of the skin or both, capillary atony and slowing of blood in peripheral capillaries are further increased, resulting in a livedo reticularis pattern in annular rings about central paler areas. Cold causes an increased vasoconstriction of the arteries and arterioles, resulting in an intensification of the livedo. When the periph-

eral capillaries are only temporarily atonic and dilated, and the arteriolar supply is only temporarily reduced, the transient cutis marmorata results; but if the changes are more or less permanent, then true livedo reticularis is produced. On elevation of the affected parts, the livedo decreases if the venules draining the areas are patent and can drain the stagnant blood from the capillaries. Warmth and sympathectomy reduce the spasm of the arteries and arterioles and thus reduce the degree of discoloration.

These observations and interpretations are attractive. As in Raynaud's disease and acrocyanosis, however, the basic factors underlying the vascular disturbances and manifestations are unknown. Whether or not the defect is primarily one of local vessel fault or one of sympathetic nerve disturbance, and whether or not localization of the disorder to these sites is determined by congenital or acquired mechanisms, are not known. Relief of livedo reticularis and return to normal color has been reported following sympathectomy and also following the administration of acetyl-beta-methylcholine (22). The problems surrounding supposition of a sympathetic nerve disease as the basic disturbance are essentially as discussed for Raynaud's disease and acrocyanosis.

CAUSALGIA AND RELATED SYNDROMES. This is one of the most confused areas of all in peripheral vascular disease today. Definitions are poor; criteria for classification and diagnosis, variable; and terminology, diffuse. The unifying characteristic of this group is the development of a bizarre symptom complex following some type of injury to an extremity. This posttraumatic syndrome consists in general of pain, paresthesia, trophic changes, edema, and evidence of autonomic nervous system dysfunction. In this group of diseases are included major causalgia, minor causalgia, traumatic vasospasm, acute atrophy of bone, Sudeck's atrophy, reflex nervous dystrophy, traumatic angiospasm, posttraumatic painful osteoporosis, neurovasospastic phenomenon, chronic posttraumatic edema, posttraumatic reflex dystrophy, sympathetic dystrophy, neurovascular reflex dystrophy, atypical causalgia, posttraumatic spreading neuralgia, reflex nervous atrophy, irritative nerve lesions, sympathalgia, posttraumatic pain syndrome, peripheral acute trophoneurosis, postamputation syndrome, and traumatic neuralgia. All these terms have been employed in reports in the literature, and undoubtedly others have been used. Each term has

served to focus not only on the outstanding manifestations in each particular patient studied but also on the particular interests, specializations, and orientations of the various investigators. This type of terminology usually implies gross confusion, and such is the case. Although these syndromes have elements of both vasodilator and vasoconstrictor mechanisms, they are classified under the latter, since these manifestations are the most classic of the disorders.

To discuss the manifestations of each of the disorders listed above would be beyond the scope of this presentation. Adequate descriptions and reference sources may be found in other publications (1, 3, 19, 34, 44, 49, 53, 58, 82, 87, 89, 90, 104).

There is great overlap of the manifestations in the syndromes listed. In general they may follow any type of injury to an extremity whether minor or severe. Some investigators feel that there is a constitutional predisposition to the development of these syndromes in certain individuals. Whether or not psychogenic factors and a previous history of vasomotor instability are important has been debated.

The provoking injury usually, but not invariably, involves nerves (especially the median or sciatic) or tissues around joints (particularly the wrist or ankle). Pain and vasomotor disturbances may occur almost immediately after the injury, or be delayed and develop gradually over the next several weeks. Pain from the original injury with its associated accentuation on movement, with resulting disuse, may be important factors in the pathogenesis.

The outstanding characteristic of the causalgia syndrome is burning superficial pain. Pain is usually referred distal to the site of original injury and frequently involves the digits and the volar surfaces of the hands and feet. Hyperesthesia is a common associated complaint which may be localized to a sensory nerve, but is frequently incomplete and neither segmental nor somatic in distribution. Because of this, these patients are frequently considered to be malingerers or "neurotic." Patients at times go to extremes to protect their hyperesthetic extremities, avoiding many direct as well as indirect stimuli, even loud noises. Frequently they obtain relief from the application of moist cloths. Obviously, since the disease is posttraumatic the symptoms are usually unilateral. In later stages, however, vasomotor disturbances may spread to the opposite extremity.

The vasomotor changes are of particular interest.

Initially, the affected extremity is usually somewhat edematous, erythematous, dry, and warmer than its unaffected counterpart. The blood vessels are dilated, the rate of blood flow is increased, and local temperature and oscillometrically recorded pulsations are increased. Later, the vasodilatation subsides and vasospastic phenomena usually become prominent and remain so during the chronic stage of the disease. In this chronic stage, the skin is usually cold, hyperhidrotic, cyanotic, and atrophic. The limb may then be especially sensitive to cold and secondary Raynaud's phenomenon may be observed.

Early X-ray study reveals a spotted, often cyst-like, decalcification of the bones in the involved part. This is especially true for the ankle and wrist and the bones of the hands and feet (Sudeck's atrophy). It is considered that these changes in bone occur much too early to be explained simply as atrophy from disuse. Later in the disease, however, osteoporosis may become diffuse and difficult to differentiate from osteoporosis of disuse. There is emphasis by the patient on immobilization and disuse of the part because of pain and, therefore, disuse may be a contributing factor.

The tendency among most investigators has been to divide the syndrome into at least two subgroups: namely, *major causalgia* and *minor causalgia*. In major causalgia there is usually a history of a penetrating wound in the region of a major nerve trunk of the limb and the subsequent characteristic symptom is that of severe burning superficial pain. In minor causalgia the provoking trauma is frequently minor in type and major peripheral nerve trunks are not involved. Although there are evidences of vasomotor dysfunction and trophic changes in both the major and minor varieties, spotty osteoporosis and edema have been much more frequently seen and severe burning superficial pain less frequently seen in the latter.

Successful treatment with marked or complete relief of symptoms has been reported to follow intra-arterial or orally administered sympatholytic drugs, paravertebral sympathetic nerve blocks, and sympathectomy (82). In fact, success with these measures may be strong ancillary factors in substantiating the diagnosis.

The pathogenesis of the causalgia syndromes is unknown and it would be profitless to discuss the many proposed theories. These are available in other publications (1, 3, 19, 34, 49, 53, 58, 82, 87, 89, 90, 104). They are interesting and thought-provoking but largely unfounded. The whole field is complex and

confusing, but it might be helpful to indicate interesting factors which have pathogenic relationships to the disease.

Though sometimes very minor, tissue trauma is a regularly associated factor. Fractured bones with injury to adjacent nerves, surgery, tight bandages and dressings, automobile accidents, falls and the like seem to produce the syndrome.

Afferent neural conducted impulses (possibly abnormally integrated, distributed or modulated) must certainly be factors. Pain is perceived by the patient and is frequently the outstanding symptom. That this is mediated through regular sensory-type nerves is probable, but debatable.

Efferent neural conducted impulses apparently play a part. Most probably a large proportion is mediated through the sympathetic nervous system. As in the afferently conducted impulses, these may be integrated, distributed, or modulated abnormally. Vasomotor disturbances are paramount and relief with sympathetic block or sympathectomy is frequent.

Afferent neural conduction and efferent neural conduction imply, but do not prove, since they may be dissociated phenomena, that some reflex arc is involved in the disturbance. The level in the nervous system at which this occurs and how it functions is not clear. It could be an axon reflex, a short-circuiting in a peripheral nerve trunk, or an arc in the spinal cord at segmental or higher levels or even in the vasomotor centers or higher. Furthermore, the integration, distribution, and control, as well as the modulation of the frequency, intensity, and time course of the action potential of the impulses may be abnormal in causalgia. This phase of the pathophysiology has been neglected and needs investigation.

Blood vessel reactions are apparent from the preceding discussions but exactly how they are induced is unknown.

The keynote of the causalgia syndromes is that the magnitude of the resulting physiologic and anatomic manifestations are out of proportion to the magnitude of the provoking injury. This implies altered responsiveness on the part of the body to trauma.

To integrate all the observed or apparent manifestations of the causalgia syndromes into one unified theory is difficult at the present time. Lewis (49) had interesting ideas concerning the mechanisms of pain and vasodilatation in the syndrome. He referred to evidence from Tinel showing that section of the nerve distal to the responsible lesion may relieve the causalgic pain when section proximal to the lesion had already failed to do so. He further noted that

when a normal cutaneous nerve or the posterior nerve root is cut and its distal end excited electrically, that the corresponding area of skin reddens and becomes hotter than previously ("antidromic effect") and a burning itching pain is produced. Lewis believed that this resulting vasodilatation in the skin is produced by a local release of a histamine-like substance. He thought that the substance released affects overlapping nerve endings in the area. Thus, analogous pain impulses in causalgia might be conveyed back along these intact paths as well as along the injured nerve. Lewis thus concluded that the erythema and heat stage of causalgia was an antidromic effect produced by distal stimulation of the injured nerve and that this was in accordance with the observations of Tinel. Lewis' theory does not explain all the findings, however, such as the vasoconstrictor phenomena and the relief with interruption of the sympathetic nerve supply.

One theory which has recently been attractive to many investigators serves in part to explain the pain and its relief with sympathectomy (19). In general, it might be conceived as follows: In a zone of nerve injury, the insulating factors that normally keep one nerve fiber from interfering with its neighbor are defective. Thus, efferent impulses might cross-stimulate afferent fibers resulting in sensory disturbances and pain. Regarding the efferent impulses, the autonomic fibers logically would be the most offensive in the damaged nerve since these have continuous vasotonic activity. Therefore, during periods of increased vasomotor activity there would be more cross stimulation in the injured nerve and thus more pain. Increased pain might thereby result in increased sympathetic nervous activity and thus propagate a vicious cycle.

The preceding theory may adequately explain changes occurring unilaterally in the injured limb, but would be inadequate to explain the extension of vasomotor dysfunction into the contralateral member. Thus, some higher source of nervous dysfunction might well be involved. Further, it is accepted by some that chronic neural irritation, especially if excessive, is capable in some way of changing the normal behavior of the neurons within the central nervous system and of eventually modifying the pattern of excitation registered in the conscious levels (87). This may be an expression of disturbance in integration, distribution, and modulation of the action potentials of the nerve impulses within the central nervous system. There are occasional patients with causalgia unrelieved by peripheral nerve sec-

tion, section of the posterior roots or sympathectomy. It has been assumed that these patients represent examples of "thalamic dysfunction."

Other theories involving higher centers are of interest, but will not be expanded. For example, it has been suggested that an irritative focus in the extremity produces afferent impulses over sensory nerves to the spinal cord which results in continual impulse discharges and nervous disturbance in this zone. This results in stimulation of the elements of the lateral and anterior horns, which then produce the characteristic peripheral signs (53). A theory proposed by Leriche (44) involved reflex overactivity of the central vasomotor center.

Some theories of note have suggested involvement of afferent sympathetic nerve fibers. Of interest in this regard are studies by Kuntz (42) demonstrating afferent spinal nerve fibers which traverse the sympathetic trunk and communicating rami. Stimulation of appropriate nerves results in conduction of pain impulses by these afferent fibers which appear to be distributed chiefly in relation to blood vessels rather than to the skin and muscles of the extremity. Whether or not these phenomena function in the causalgia syndromes is unknown, but relief of pain by sympathectomy might be explained by such mechanisms.

MISCELLANEOUS STATES. *Spasm of major arteries.* Spasm of a large artery is initiated by some type of trauma in or near the artery. The initiating trauma is usually a severe penetrating injury such as a gunshot wound, but it may be provoked by contusing or crushing injuries even though the artery itself is not directly involved in the injury. The spasm may be sufficient to occlude the lumen completely. The spasm may be limited to a small isolated discrete segment of the artery or it may involve a long segmental length including the orifices of many collateral arteries (3).

The exact mechanism of this type of spasm is not clear but the "myogenic" factor or the inherent property of smooth muscle to contract when directly traumatized appears to be paramount. It has been shown experimentally that local segmental spasm in large arteries can be produced by mechanical trauma irrespective of the presence of the adventitia or nerve supply (38). These facts are in accordance with observations that this type of spasm usually cannot be released with periarterial injections of local anesthetics, sympathetic nerve interruption, periarterial nerve stripping, or even by amputation of the involved extremity above the site of the arterial

spasm (3, 13, 26). It has been shown, however, both experimentally and clinically, that direct application of a 2.5 per cent solution of papaverine to an artery will relieve traumatic spasm in the majority of instances (39). The mechanism of this response is unknown.

Vasoconstrictor mechanisms in acute arterial occlusion. The changes which occur after acute circulatory arrest have been presented in a preceding section. It is not the purpose of this discussion to present the clinical signs and symptoms nor the pathogenesis of events leading to acute circulatory arrest, which include occlusive arterial disease, thrombosis, and embolism. Arteriosclerosis, intravascular clotting, and embolism are discussed in other chapters of this *Handbook*. The purpose of the present discussion is to indicate, briefly, concepts concerning possible vasoconstrictor mechanisms which operate in acute arterial occlusion.

The obvious factor in acute arterial occlusion is acute impairment of blood flow through the arterial lumen. Studies suggest, however, that this is not necessarily the major cause of the resulting profound ischemia associated with acute arterial occlusion, since only mild to moderate degrees of ischemia may be produced when a comparable peripheral artery is ligated. The implication then is that a superimposed functional disturbance must be operative in pathologic occlusion.

It has been considered that reflex vasospasm of the distal portion of the artery and the collateral arteries is mediated in the efferent arc through the sympathetic nervous system (3, 87). This has been the basis for recommendation of prompt sympathetic interruption in patients with acute arterial occlusion (87). Experimental work has shown, however, that the superimposed diminution in blood supply affected by spasm and inadequate dilatation of collateral arteries is temporary and spontaneously disappears in a few hours (31, 64). Several investigators (3) have postulated that the spasm in collateral arteries, if prolonged, produces degenerative changes in the intima of distal arteries and veins which in turn provokes widespread vascular thrombosis with the resultant organic obstruction to flow even after the spasm disappears. This would account for progression to complete irreversible circulatory arrest in some patients. However, when spasm has not been severe or prolonged, a satisfactory collateral circulation may be established permitting the limb to survive (3).

Some experimental studies on the mesenteric

vascular responses in young dogs are of interest (56). After acute arterial occlusion the artery developed severe spasm whereas the vein exhibited a mild degree of spasm. On release of the occlusion there was a period of residual spasm in artery and vein. Sympathectomy abolished both the arterial and venous spasm during occlusion as well as after release. Papaverine administered during the arterial occlusion had no effect on the arterial spasm, but after release of the occlusion the residual spasm was abolished.

Recent studies, however, have cast considerable doubt on the significance of diffusely distributed vasospastic phenomena in response to acute arterial occlusion in man. Compensatory mechanisms in response to sudden arterial occlusion have been the subject of a recent report on clinical, pathologic, and experimental observations by Wessler *et al.* (102). They noted that three major important compensatory phenomena follow sudden arterial occlusion, namely, clot fragmentation, clot lysis, and function of preformed inter-arterial collateral anastomoses. The authors considered that clot fragmentation and clot lysis, although not disproving the role of "spasm," provide an alternative to the concept of release of spasm as an explanation for the occasionally witnessed sudden relief of arterial insufficiency in some patients. The gradual enlargement of anastomatic channels, bypassing complete obstructions, accounts for the delayed and gradual improvement (even with return of distal pulsatile flow) observed in some patients weeks to months after the initial occlusion. The authors further stated that unlike embolectomy, blockage of autonomic nervous supply for the relief of ischemia, secondary to arterial occlusion, has neither a sound physiologic rationale nor satisfactory clinical documentation of its efficacy (102). Based on their own (102) and other studies (76) they found little evidence that vessels in the ischemic zone are in spasm in organic arterial insufficiency.

More recent observations by Hardy & Tibbs (33) have further minimized the role of diffuse "spasm" in acute arterial thrombosis. These authors emphasized that a healthy artery is normally in a state of considerable elastic distention and that when occluded the vessels distal to the occlusion become narrow from "elastic recoil." Apparently this recoil has been the basis for the erroneous diagnosis of diffuse arterial "spasm." Patients are described (33) in whom the distal arteries remained contracted and pulseless after embolectomy, and in whom a residual "consecutive" clot was found. When this residual clot was removed

completely by retrograde irrigation, the "spasm" disappeared and pulsation returned.

Regardless of the above and other arguments, it is impossible to state dogmatically whether or not arterial "spasm" is significant in the pathophysiology of the circulation in acute arterial occlusion. The suggestion that a powerful vasoconstrictor substance (possibly serotonin) is released from a fresh thrombus and that it causes spasm of the affected vessel and adjacent collaterals (25, 83, 101) needs further study.

Vasoconstrictor mechanisms in chronic arterial occlusion. This topic has caused considerable discussion, especially among surgeons who advocate sympathectomy in the treatment of chronic arterial occlusive disease. One major basis for this suggestion has been the thesis that even if superimposed arterial spasm is not of pathogenic importance, sympathectomy is of benefit because it reduces normal arterial "tone" causing arterial dilatation and fostering collateral circulation. Particularly with respect to muscle circulation, neither experimental nor clinical evidence in man justifies pursuing this topic further.

Vasoconstrictor mechanisms in collagen diseases and diseases of the fine blood vessels. These diseases and diseases of "immune" mechanisms are on the forefront of medicine today. Much progress has been made in understanding these conditions. In general, the "collagen diseases" include lupus erythematosus, scleroderma, dermatomyositis, periarteritis nodosa, rheumatic fever, and rheumatoid arthritis. Also included among these diseases are thrombotic thrombocytopenic purpura, multiple forms of "vasculitis" (see APPENDIX) and several other disease states. The present day concept of the collagen diseases is that they represent diseases which primarily involve connective tissue structures. Since connective tissue is ubiquitous the manifestations of these diseases are protean. Regardless of terminology, there is no reason to assume that the collagen fiber is the only structure involved in these processes, but rather that the disease is generalized including all connective tissue constituents such as reticulum fibers, elastic fibers, ground substance, and all related cells such as fibroblasts, histiocytes, lymphoid elements, plasma cells, and mast cells.

Even to attempt to discuss briefly the generalities of this group of diseases would be beyond the scope of this presentation. Numerous sources are available in the literature. A brief review with particular emphasis on cardiovascular manifestations has been published (97). The blood vessels certainly are the

major shock organs of these diseases. It is likely that the vasculitis is responsible for a great portion of the manifestations of the various disease entities. Any type of vessel may be involved, but the fine blood vessels are usually major participants. Pathological changes include subendothelial fibrinoid degeneration, fibroblastic proliferation, intimal thickening, varied inflammatory responses, and thromboses.

From the pathophysiologic standpoint the vascular manifestations probably result in greatest part from organic structural change and occlusion. That a functional vasospastic component may be superimposed, however, has been proposed. It has been stated that angiitis of the fine acral vessels is particularly apt to give rise to vasoconstriction both reflexly and by direct stimulation of the vessel network (21). The organic changes plus the "spastic" factors lead to agglutination of the cellular elements of blood in the fine vessels in the distal reaches of the circulation, which is an effective precursor of tissue necrosis. It is impossible to quantitate the degree to which functional vasospasm contributes to the pathogenesis of these diseases. Vasospasm probably exists to some degree as suggested (but not proved) from the frequent association of secondary Raynaud's phenomenon (as high as 25% in some series).

Scleroderma (progressive systemic sclerosis). The terms sclerodactylia, acrosclerosis, and scleroderma (progressive systemic sclerosis) have been introduced in the section on Raynaud's phenomenon; the collagen diseases in general have been discussed above. Because of its importance, scleroderma or progressive systemic sclerosis is discussed further.

Scleroderma is a systemic disorder which involves connective tissue of skin, muscles, tendons, fascia, and all internal organs. Its outstanding manifestation is a generalized increase in collagen fibers (97).

As with other collagen diseases, the etiology of scleroderma is unknown. It affects both the white and Negro races (74), is more common in females,



FIG. 6. Severe scleroderma.

and usually occurs during early adult life and middle age.

Many organs of the body may be involved. Thickening of the skin with tightening, increased rigidity, and reduced distensibility, involving the face, extremities, and trunk produce a characteristic appearance (fig. 6). In the early stages of the disease the skin may be edematous, but later it characteristically becomes firm and nondistensible, with areas of hyperpigmentation and hypopigmentation, and the joints become stiff and contracted. Calcification of tissues, absorption of the terminal phalanges, atrophy of the fingertips, deformed nails, and cutaneous ulcers may occur. The face may offer a striking appearance being tight, expressionless, and masklike without wrinkles. The features are pinched, the nose is pointed, and there is difficulty in smiling and opening the mouth. Acral vasomotor disturbances such as color changes, coldness, hyperhidrosis, and Raynaud's phenomenon are not infrequent.

Histologic sections through affected skin show that the Malpighian layer is atrophic. The deep layers of the skin show increased fibrosis which extends into the subcutaneous tissues. It may extend into muscles of the limbs and may bind the skin of the fingers to bone. Blood vessels are entrapped in the dense fibrotic change. The feet may be involved but the hands show by far the most extensive change.

Involvement of the gastrointestinal tract is common, especially the esophagus, frequently the small bowel and occasionally the colon. This may produce obvious functional changes in these organs. Joint involvement may mimic rheumatoid arthritis and skeletal muscle involvement with atrophy and fibrosis may resemble dermatomyositis. Pulmonary involvement is very common with peribronchial and interstitial fibrosis and destruction of alveolar walls.

The vascular manifestations of the disease may be widespread. There is thickening of vessel walls, perivascular fibrosis, intimal proliferation, obliterative vasculitis, thrombosis, fibrinoid necrosis, and cellular infiltrations with polymorphonuclear and round cells.

Usually smaller vessels are predominantly affected, but lesions may be encountered in any vessel of the body. The coronary, pulmonary, dermal, and renal vascular beds are notable participants in this vascular disease. Primary changes in the myocardium, apart from the involvement of myocardial vessels, are frequent. There is interstitial fibrosis, myocardial degeneration, endocardial, epicardial and pericardial fibrosis, and ventricular dilatation and hypertrophy.

Obviously, clinical manifestations may be multiple and varied. Renal involvement may cause albuminuria, hematuria, and hypertension. Myocardial disease may present any of the findings seen in congestive heart failure. Pulmonary involvement may be expressed as respiratory alveolar-capillary block syndrome, fibrosis and emphysema, obstructive and restrictive ventilatory dysfunction, hypoxia, carbon dioxide retention, pulmonary hypertension, polycythemia, cor pulmonale, and the like. Thoracic involvement with the tight constricting skin may produce hypoventilation and circulatory dysfunction.

All the above and other changes in scleroderma are obviously of importance to a discussion of the peripheral circulation because, potentially, they may all contribute to disordered peripheral vascular physiology. To quantitate their effects, however, would be a difficult or impossible task. In addition to these general effects, more direct factors in scleroderma may influence vascular function. Comments made in the preceding section on vasculitis and collagen disease, in general, are applicable here. As noted, obliterative vascular change is probably the major factor in vascular dysfunction, but a superimposed functional vasospastic element has been suggested.

The frequent occurrence of Raynaud's phenomenon in scleroderma is of interest. It may precede, accompany, or follow the clinical disease onset. The true relationship between the two is unknown. It was long held by many that the vasomotor abnormality was of etiologic importance in the pathogenesis of scleroderma. The majority of current opinion, however, is that associated Raynaud's phenomenon is a secondary manifestation of scleroderma due to the primary disturbance in blood vessels and connective tissue. In this regard it is analogous to secondary Raynaud's phenomenon occurring in other collagen diseases.

Of the collagen diseases, however, scleroderma presents an additional unique factor in that the vessels are entrapped in a fibrotic ever-contracting, poorly distensible environment. Thus, in addition to intravascular occlusion there may be, in effect, extravascular constriction or strangulation (59, 81, 92). Greatly increased pressures have been found in the subcutaneous tissue in patients with scleroderma. Studies have shown tissue pressure values up to 320 mm of water in patients with scleroderma, whereas normal persons do not exceed 54 mm (92). These added factors may be of significance in explaining the altered peripheral vascular function in scleroderma. In this disease, reduced skin temperature and decreased digital pulsations are common. That these changes are largely structural or organic in origin is suggested by failure of these parameters to return to normal after use of sympatholytic drugs or inhibition of sympathetic tone through nerve block or sympathectomy.

Vasoconstrictor mechanisms in acute thrombophlebitis. The clinical manifestations of thrombophlebitis have been adequately described in a number of publications (1, 3, 87, 104) and will not be repeated here. Mechanisms of intravascular clotting are discussed elsewhere in this volume.

Perhaps a few words regarding terminology are in order. It has been common practice in the past for clinicians to use the terms "thrombophlebitis" and "phlebothrombosis" to represent two different and distinct clinical syndromes (69). Thrombophlebitis was considered to represent a rather intense inflammatory reaction in the involved vein with a more firmly attached thrombus. Although it produces a more dramatic local reaction, it was considered to be less dangerous, since there was less likelihood for emboli to break from the thrombus. In contrast, phlebothrombosis, although bland with respect to local reactions and manifestations, was considered to

be the more lethal, since the associated loosely attached thrombus was more predisposed to break into emboli. Recent experimental and clinical evidence suggests, however, that phlebothrombosis is merely the silent forerunner of thrombophlebitis and that the two diseases are stages of the same process (14, 29, 55).

Other terminology is dependent upon whether or not superficial or deep veins are involved for which the terms superficial and deep thrombophlebitis are applied. The process of course is named according to the particular vein or veins involved. When infection is a predominant accompaniment, the term "septic" or "suppurative" thrombophlebitis is applied.

An interesting rare variant of thrombophlebitis, the Trousseau syndrome, or "migratory thrombophlebitis," should perhaps be mentioned. This disease may involve either superficial or deep veins, in one or more sites, either concurrently or separated by considerable lengths of time. The importance of this syndrome is related to the frequency with which underlying serious disease is present, especially, thromboangiitis obliterans, polycythemia vera, occult carcinoma (usually of the stomach, pancreas, or lung), or collagen disease (14).

The outstanding finding in typical acute superficial thrombophlebitis is pain and tenderness over the involved area, but embolic phenomena may occur. Deep thrombophlebitis especially predisposes to embolism. In deep thrombophlebitis the main physiologic disturbance is obstruction to venous blood flow. Pain of various types may be a feature and is helpful in diagnosis, but edema is the most objectively demonstrable physiologic alteration. The degree of this disturbance is obviously dependent on the size and location of the involved vein, the extent of the thrombus, and the adequacy of collateral circulation. When a large trunk such as the iliofemoral or axillary vein is involved with a long thrombus also compromising collateral flow, considerable obstruction to venous flow may occur and the increase in venous pressure may be marked. This is in contrast to simple ligation of a venous trunk in which collateral circulation is not adversely affected.

Edema formation, secondary to venous occlusion in thrombophlebitis, is much more than a simple process of increased venous pressure with resultant increase in mechanical transudation of fluid into the tissue space, but this factor seems to be important. The importance of associated lymphatic obstruction

in thrombophlebitis in the production of the edema is debated and not yet clarified. Certainly, fibrotic reactions in long-standing edema with a high protein content of the extracellular fluid impairs lymph flow.

Appropriate to the present discussion are studies concerning possible vasomotor or sympathetic factors in the pathogenesis of the manifestations in thrombophlebitis. That arterial spasm may occur in some patients with deep vein thrombophlebitis is not denied, but whether or not it is a significant factor in most instances is debatable. In some patients during the acute stages of the disease spasm may be so severe that pulsations in the large arteries disappear for several hours. Several patients with actual ischemic gangrene have been reported. The terms "phlegmasia alba dolens" and "phlegmasia cerulea dolens" have been used in some of these patients to describe the associated color changes thought to be due to accompanying arterial spasm.

Some studies (68) suggest that vasoconstrictor impulses are initiated by the thrombosed segment of vein which produces spasm of both arterioles and venules in the distant portions of the limb. Experimental and clinical evidence has been presented in favor of the idea that the thrombosed venous segment initiates a detrimental spinal reflex arc with the sympathetic nerves as its efferent arm. The induced arterial, arteriolar, venous, and venular spasm was said to propagate edema formation by increased venous pressure with augmentation of filtration pressure, by relative anoxia of capillary endothelium with increased fluid transudation and by retarded lymph flow secondary to reduced "pumping action" from the arterial and arteriolar vessels in spasm. Rather dramatic clinical improvement in patients following paravertebral sympathetic blocks, both in subsidence of pain as well as edema, has been reported.

Subsequent experimental studies on mesenteric vessels of young dogs support some of these concepts (56). It was found that after acute occlusion of the main stem vein the artery reflexly underwent spasm, whereas the vein became moderately dilated. On release of the occlusion there was a period of residual arterial constriction, whereas the vein returned to its preocclusion caliber. After sympathectomy, however, it was noted that all reflex arterial constriction, as well as the residual arterial constriction that followed release of the occlusion, were abolished. It was noted that during occlusion the vein became dilated to a diameter exceeding that of the control. Although

these experiments tend to lend support in part to the concept of reflex arterial constriction, the latter observation regarding venous dilatation is not in accordance with the concept of venous or venular constriction. This factor in thrombophlebitis had been difficult to accept in the light of the intense congestion and obvious distention of the small veins (3).

The theory that associated vasospasm in thrombophlebitis is a frequent and important pathophysiologic factor is intriguing but more definitive experimental work is required for confirmation and general acceptance in clinical medicine.

Vasodilative Syndromes

Vasodilatation as an important vascular response is seen in a number of physiologic states such as thermoregulation, tissue inflammatory response, reactive hyperemia, early stages of causalgia, and the like, but the cardinal condition which concerns us here is erythromelalgia.

ERYTHROMELALGIA (ERYTHERMALGIA). Early contributors to the literature of this disease state were Graves in 1834 (63), Mitchell in 1872 (63), Cassirer in 1912 (12), and May & Hillemand in 1924 (57). Significant contributions after that time include the work of Brown in 1932 (7), Lewis in 1933 (45), and Smith & Allen in 1938 (91). Since then, little definitive work has been done and published on erythromelalgia.

Erythromelalgia is a vasodilative syndrome characterized by episodes of erythema, increased heat and pain involving the hands and especially the feet. It has been placed into primary and secondary categories. "Primary erythromelalgia" occurs in otherwise healthy individuals who manifest no detectable evidence of organic disease of the nervous or vascular systems. Analogous to Raynaud's phenomenon, "secondary erythromelalgia" occurs in association with or as a secondary symptom complex of some other primary disease, such as hypertension, occlusive organic vascular disease or polycythemia. Gout, organic neurologic disease, frostbite, immersion foot, trenchfoot, infectious diseases, and heavy metal poisoning are also incriminated.

The mechanism of erythromelalgia is unknown and the pathology has not been clarified. Symptoms usually start in middle age or later and may affect either sex. It is apparently rare in the Negro (74).

The clinical picture may be quite dramatic. The main complaint is usually burning pain in the extremities, especially in the feet and frequently in the hands. Occasionally the disturbance may extend as high as the knees or thighs. The patient usually complains that the distress affects primarily the balls of the feet and tips of the toes or corresponding parts of the hand. It may last from a few minutes to several hours. Usually the patient relates aggravation by dependency of the part, by warmth, accentuation during summer months, relief by cold and elevation of the part, and lessened symptoms during winter. Attacks may be precipitated by exercise which increases the warmth of the skin. For unknown reasons, dry heat seems to be more provocative than wet heat at the same temperature. The discomfort may start as a "pricking" paresthetic feeling then progress to a more typical severe burning pain. During the subsidence of the episode the pricking stage may again be noticed. In the primary disease, neurological examination is negative and examination of the peripheral vasculature shows no evidence of occlusive arterial disease. Trophic changes, ulceration, and gangrene are quite rare, though some swelling may be evident in the involved extremities.

What is known of the pathophysiology of this syndrome is interesting. The most important part of this syndrome is its intimate relationship with the temperature of the skin. Lewis (45) has designated a "critical point" in skin temperature at which this syndrome may be produced in susceptible individuals. It usually is around 32° C (range, 31 to 36° C). With temperatures higher than this critical point, the distress continues and with temperatures lower than this point the distress disappears (3, 91). The temperature at which the syndrome may be produced varies with different patients and also to some degree in different parts of the extremity in the same person, but in the same person the range is usually within ± 1 ° C.

Vasodilation per se seems to be an important vascular factor in the production of the erythromelalgic crises. Increased blood flow is only an indirect accompaniment. Thus, the syndrome may be produced by warming the extremity to the critical level, and the symptoms continued even though blood flow is arrested by an inflated constricting blood pressure cuff. This is so, provided the skin temperature is maintained at levels equal to or greater than the critical point.

As Lewis has pointed out, however, although

vasodilation may be the essential vascular reaction, it alone is not enough to explain the clinical state, since an equivalent degree of vasodilatation may occur in asymptomatic normal subjects in response to warmth or exercise. Thus, he concluded that the essential abnormality was a hypersensitive state of the cutaneous pain fibers to heat or tension (by dilated and engorged vessels), i.e., a "susceptible state" of the skin. Thus, he suggested that a chemical substance liberated into the skin served as the immediate stimulus to the nerve endings and supported this by the observation that the pain of the erythromelalgic skin was prolonged or intensified by arresting the circulation to the part.

The essential vessels involved in the vasodilatation are not definite, but it seems that all small vessels participate. During a typical attack, the accompanying features of vasodilation may be observed. In addition to increased temperature of the skin, there may be increased amplitude of arterial pulsation, throbbing sensations, increased elimination of heat, and increased content of oxygen in the returning venous blood. The affected part assumes a deep, dusky red color. The dusky color of the skin which indicates a low oxygen content of small vessel blood is of interest in light of the high oxygen content of returning venous blood. An explanation offered for this is arteriolar-venous shunting of some of the peripheral flow through open arteriovenous anastomoses (91).

Other observations are of interest (3, 91). If the skin temperature is slightly lower than the critical point, distress may be induced by artificially increasing the venous pressure by a proximal constricting blood pressure cuff inflated to a pressure less than arterial pressure or by holding the part below heart level to produce venous congestion. Similarly, symptoms may be lessened if an extremity is elevated even though the skin temperature remains unchanged. In addition, direct pressure on the skin of the involved area may cause relief.

A vasoconstrictor factor has been suspected in some patients during intervals when they are free of the burning distress. This is manifested as local coldness and cyanosis or pallor of the skin during these pain-free periods. Some patients have been reported to suffer from Raynaud's phenomenon when cold and erythromelalgia when warm.

In diagnosis of erythromelalgia, one must exclude the burning sensations in the extremities of patients who are suffering with peripheral neuritis, occlusive arterial disease, and other states, but who do not

have erythromelalgia either primary or secondary. In these patients the skin temperature is frequently low (especially in organic vascular disease) or normal, and the intimate relationship of distress to a critical thermal level is not apparent. Further, it should be noted that in organic vascular disease elevation frequently accentuates symptoms and causes the involved part to assume a pale and waxy color, whereas in erythromelalgia color largely persists on elevation and the symptoms may be somewhat alleviated. In establishing a diagnosis of erythromelalgia it is essential to demonstrate that skin temperature and the distress are related. For this purpose, the patient's reaction and skin temperature are observed while the temperature is raised either by reflex vasodilatation or by direct application of heat.

One other interesting fact bears comment. Acetylsalicylic acid, in an oral dose of as little as 0.65 g, may produce marked and persistent relief in erythromelalgia for as long as several days. The mechanism of this response is unexplained, but it may be related to effects on the local release of bradykinin.

In the pathophysiology of erythromelalgia, although the vascular responses to temperature are in part well established, the mechanisms that induce these responses are unknown. Whether the basic defect is in the nervous system or in the blood vessels themselves is not clear. Regardless of the site, the mediators involved need study. Furthermore, it is not known whether or not the disturbance is congenital or acquired. The possible contributions of vasoactive humoral agents and the vasodilator nerves and the mechanisms of their actions are also unknown. It may be worthwhile, however, to direct attention to the renewed interest in vasodepressor polypeptides, in particular bradykinin. Depressor polypeptides have been the subject of a recent review (35) and their possible physiologic functions are covered elsewhere in this volume. Further study might well incriminate bradykinin as an important factor in the pathophysiology of peripheral vascular disease, not only in erythromelalgia, but in numerous other vasodilator reactions.

Mechanisms in Other Vascular Diseases

In the preceding discussions it was not possible to survey the pathophysiologic mechanisms of many other diseases of the peripheral vascular system. The reader may obtain insight into the scope of the problem by referring to the APPENDIX of this chapter.

APPENDIX

CLASSIFICATION OF PERIPHERAL VASCULAR DISEASE

Diseases Affecting Primarily the Arteries and Arterioles

I. FUNCTIONAL CONDITIONS

A. Vasoconstrictor

1. Raynaud's syndrome (primary Raynaud's disease)
2. Raynaud's syndrome (secondary)
 - a. Traumatic vasospastic syndrome
 - b. Neurovascular mechanisms
 - (1) Shoulder girdle syndromes
 - (a) Scalenus anticus
 - (b) Cervical rib
 - (c) Costoclavicular
 - (d) Hyperabduction
 - (e) Thoracic outlet
 - (f) Malposition
 - (g) Pectoralis minor
 - (2) Spondylitis
 - (3) Neuritis
 - c. Secondary to organic vascular disease
 - (1) Arteriosclerosis
 - (2) Syphilitic arteritis
 - (3) Thromboangiitis obliterans
 - (4) Thrombotic or embolic occlusion
 - (5) Other occlusive arterial disease
 - d. Secondary to intoxications
 - (1) Arsenic
 - (2) Ergot
 - (3) Lead
 - (4) Nicotine
 - (5) Tobacco
 - e. Scleroderma and acrosclerosis
 - f. Miscellaneous mechanisms (e.g., rheumatoid arthritis, lupus erythematosus, cold injury, and other factors listed in Category 5 below)
3. Acrocyanosis
4. Livedo reticularis
 - a. Idiopathica
 - b. Symptomatic livedo reticularis
 - (1) Questionable factors

Rickets, mongolism, various endocrinopathies, malnutrition, varicose veins, other peripheral vascular diseases, infectious diseases, intoxications, congenital vascular defects, ectodermal abnormalities, cirrhosis of the liver and other unusual diseases, and neural disorders
 - (2) Probable factors
 - (a) Hypertension
 - (b) Nervousness and emotional instability
 - (c) Arsenic or lead poisoning (?)
 - (3) Purported causes
 - (a) Tuberculosis
 - (b) Syphilis
 - (c) Periarteritis nodosa and allergic cutaneous vasculitis
 - c. Cutis marmorata

5. Vasospasm, secondary to
 - a. Lesions of peripheral nerves
 - b. Lesions of brain and spinal cord including poliomyelitis, prolapsed nucleus pulposus, hemiplegia, tumors, multiple sclerosis, epileptic equivalent, spinal bifida, spinal arthritis, lesions of midbrain and internal capsule, etc.
 - c. Thrombophlebitis
 - d. Embolism
 - e. Thrombosis
 - f. Trauma
 - (1) Posttraumatic reflex sympathetic dystrophy
 - (2) Major causalgia
 - (3) Minor causalgia
 - (4) Sudeck's atrophy
 - (5) Posttraumatic osteoporosis
 - (6) "Vibrating-machine disease"
 - (7) Shoulder-hand syndrome
 - (8) Crutch arteritis
 - (9) Metabolic, adynamic and hormonal, including rheumatoid arthritis, malnutrition and asthenia, terminal rheumatic heart disease, hypothyroidism, castration, menopause, hypoglycemia, Addison's disease, polycythemia, cold hemagglutination and cryoglobulins, leprosy, etc.

B. Vasodilator

1. Erythromelalgia, primary
2. Erythromelalgia, secondary to
 - a. Polycythemia vera
 - b. Arteriosclerosis
 - c. Thromboangiitis obliterans
 - d. Hypertension
 - e. Miscellaneous factors: trauma, gout, frostbite, immersion foot, trenchfoot, infectious diseases, heavy metal poisoning, etc.

II. ORGANIC CONDITIONS (STRUCTURAL)

A. Occlusive (organic)

1. Arteriosclerosis
 - a. Atherosclerosis
 - b. Atherosclerosis
 - c. Atherosclerosis obliterans
 - d. Medial (Mönckeberg's) arteriosclerosis
 - e. Arteriolosclerosis and hypertensive ischemia
 - f. Combined
2. Thromboangiitis obliterans
3. Arteritis (inflammatory diseases) and arteriolitis
 - a. Disseminated arteritis
 - b. Erythema induratum
 - c. Erythema nodosum
 - d. Nodular panniculitis
 - e. Nodular vasculitis
 - f. Temporal arteritis
 - g. Syndromes of necrotizing and/or allergic vasculitis
 - (1) General syndromes
 - (a) Purpura rheumatica
 - (b) Schonlein-Henoch syndrome
 - (c) Allergic angiitis
 - (d) Anaphylactoid purpura
 - (e) Necrotizing vasculitis
 - (f) Periarteritis nodosa of hypersensitivity

- (g) Wegener's granulomatosis and lethal midline granuloma of the face
- (2) Cutaneous syndromes
 - (a) Acute parapsoriasis
 - (b) Nodular allergic of Gougerot
 - (c) Allergic granulomatosis
 - (d) Allergic microbid
 - (e) Erythema elevatum diutinum
 - (f) Malignant atrophic papulosus of Degos
- 4. Ergotism
- 5. Collagen diseases
 - a. Dermatomyositis
 - b. Disseminated lupus erythematosus
 - c. Periarthritis nodosa
 - d. Scleroderma
- 6. Hypertensive vascular disease
- 7. Arterial thrombosis
 - a. Associated with infectious diseases
 - b. Associated with blood dyscrasias
 - c. Secondary to trauma or compression (Volkmann's contracture, shoulder girdle syndrome)
 - d. Secondary to surgery
 - e. Associated with parturition
 - f. Associated with cardiac insufficiency
 - g. Associated with slowed blood stream
 - h. Associated with exposure to radiation
 - i. Idiopathic
- 8. Abscess of wall of artery
- 9. Cold injuries
 - a. Chilblains (pernio)
 - b. Cold urticaria
 - c. Frostbite
 - d. Immersion foot
 - e. Trenchfoot
- 10. Livedo reticularis
- 11. Arterial embolism
 - a. Thrombus
 - b. Fat
 - c. Air
 - d. Bacterial
 - e. Neoplastic
 - f. Fungus
 - g. Inorganic substances
- 12. Ainhum
- 13. Blood agglutination
 - a. Dyscrasias (polycythemia, leukemia, thrombotic thrombocytopenic purpura)
 - b. Cold reactions (possible cold agglutinins, cryoglobulinemia)
 - c. Idiopathic (necrotizing acrocyanosis)
 - d. Massive venous thrombosis
- B. Nonocclusive (organic)*
 - 1. Aneurysm
 - a. Congenital
 - b. Syphilitic
 - c. Arteriosclerotic
 - d. Mycotic
 - e. Traumatic
 - f. Embolic
 - g. Idiopathic
 - 2. Arteriovenous anastomosis (fistula)
 - a. Congenital

- b. Traumatic
- c. Secondary to malignancy
- d. Secondary to bacterial infections
- e. Secondary to fungus infections
- 3. Congenital anomalies of artery
- 4. Trauma of artery
- 5. Shoulder girdle syndromes
- 6. Rupture of artery
- 7. Effects of exposure to radiation
- 8. Nonocclusive arteritis

Diseases Primarily Affecting the Veins

I. FUNCTIONAL CONDITIONS

A. Spasms

II. ORGANIC CONDITIONS (STRUCTURAL)

A. Occlusive

- 1. Thrombophlebitis and venous thrombosis (phlebotrombosis)
 - a. Primary
 - (1) Thromboangiitis obliterans
 - (2) Migratory thrombophlebitis
 - (3) Essential or idiopathic, local
 - b. Secondary to
 - (1) Mechanical injury
 - (2) Muscular effort or strain
 - (3) Chemical injury
 - (4) Inflammatory or suppurative lesions (etiological agent to be indicated)
 - (5) Infectious diseases
 - (6) Severe ischemia
 - (7) Varices
 - (8) Blood dyscrasias
 - (a) Polycythemia
 - (b) Myelogenous leukemia
 - (c) Lymphatic leukemia
 - (d) Pernicious anemia
 - (e) Disturbances of blood clotting mechanism
 - (f) Other blood dyscrasias
 - (9) Cardiac insufficiency
 - (10) Carcinoma
- 2. Neoplastic invasion of vein
- 3. Venous compression by
 - a. Gravid uterus
 - b. Neoplasm
 - c. Aneurysm
 - d. Scar tissue
 - e. Scalenus anticus syndrome
 - f. Hyperabduction syndrome
 - g. Fractures
 - h. Dislocations
 - i. Increased intra-abdominal pressure (ascites)
- 4. Postphlebotic syndrome

B. Nonocclusive

- 1. Varicose veins
 - a. Primary
 - b. Secondary to
 - (1) Posture
 - (2) Occupation
 - (3) Clothing

- (4) Proximal obstructive lesions or pressure (see II, A, 3)
- (5) Thrombophlebitis
- (6) Arteriovenous anastomosis
- (7) Hemangioma
- (8) Congenital anomalies of veins
- 2. Arteriovenous anastomosis (fistula)
 - a. Congenital
 - b. Traumatic
 - c. Secondary to malignant lesions
 - d. Secondary to bacterial infections
 - e. Secondary to fungus infections
- 3. Aberrant position of vein
- 4. Hypoplasia of vein
- 5. Phlebectasia
- 6. Periphlebitis
- 7. Phleboscrosis
- 8. Rupture of vein

Neoplasms of Blood Vessels

I. BENIGN

A. Hemangioma

- 1. Cavernous
- 2. Capillary
- 3. Plexiform
- 4. Sclerosing
- 5. Sturge-Parkes Weber-Dimitri syndrome
- 6. Von Hippel-Lindau disease
- 7. Maffucci's syndrome
- 8. Multiple hemangiomas and chondromata (Kast's syndrome)

B. Glomus

C. Telangiectasia

- 1. Hereditary hemorrhagic
- 2. Senile
- 3. Simple
- 4. Spider
- 5. Papillary varices

II. MALIGNANT

A. Ewing's sarcoma

B. Hemangioendothelioma

C. Hemangiosarcoma

D. Kaposi's sarcoma

- (3) Fungus
- (4) Erysipels
- b. Mechanical, chemical and physical
 - (1) Abrasions
 - (2) Burns
 - (3) Chemical irritation
 - (4) Lacerations
 - (5) Trauma
 - (6) X-ray
- c. Granulomata
 - (1) Lymphogranuloma
 - (2) Syphilis
 - (3) Tuberculosis
- d. Postphlebitic
- e. Surgery
 - (1) Removal of lymph nodes
 - (2) Removal of lymph vessels
- f. Neoplastic invasion of lymph nodes
 - (1) Endothelioma
 - (2) Hodgkin's disease
 - (3) Leukemia
 - (4) Lymphangioma
 - (5) Lymphocytoma
 - (6) Lymphoma
 - (7) Lymphosarcoma
 - (8) Obstruction of thoracic duct
 - (9) Sarcoma of lymph nodes
 - (10) Reticular cell sarcoma
- g. Dependency edema

II. LYMPHANGITIS

A. Primary (idiopathic)

B. Secondary

- 1. Infection
- 2. Infestation
- 3. Trauma

III. NEOPLASMS OF LYMPH VESSELS

A. Benign

- 1. Lymphangiectasia
- 2. Lymphangioma
 - a. Simple
 - b. Cavernous
 - c. Cystic

B. Malignant

- 1. Lymphangiosarcoma

Diseases Primarily Affecting the Lymphatics

I. LYMPHEDEMA

A. Primary (idiopathic)

- 1. Congenital and hereditary (Milroy's disease)
- 2. Congenital but not hereditary
 - a. Without constricting bands
 - b. With constricting bands
- 3. Praecox

B. Secondary

- 1. Lymphangitis and lymphadenitis
 - a. Infection and infestations
 - (1) Filariasis
 - (2) Pyogenic

Diseases Affecting Primarily the Minute Vessels

I. INCREASED FRAGILITY (PURPURA) OF VESSELS

A. Thrombocytopenic purpura

- 1. Primary: idiopathic (Werlhof's) disease
- 2. Secondary
 - a. Vascular defects
 - (1) Thrombotic thrombocytopenic purpura
 - (2) Blood dyscrasias
 - (a) Acquired hemolytic anemia
 - (b) Hodgkin's disease
 - (c) Leukemia
 - (d) Malignant lymphoma
 - (e) Myeloma
 - (f) Pernicious anemia

- (3) Infections
 - (a) Bacterial
 - (b) Rickettsial
 - (c) Viral
 - (4) Splenomegaly
 - (a) Banti's syndrome
 - (b) Felty's syndrome
 - (c) Gaucher's disease
 - (d) Hodgkin's disease
 - (e) Leukemia
 - (5) Malignancy
 - (6) Drugs and chemical agents
 - (a) Allyl-isopropyl-acetyl-carbamide (Sedormid)
 - (b) Arsenic
 - (c) Benzene
 - (d) Bismuth
 - (e) Certain foods, such as orris root
 - (f) Chloramphenicol
 - (g) Dichloro-diphenyl-trichloro-ethane (DDT)
 - (h) Digitoxin
 - (i) Dinitrophenol
 - (j) Ergot
 - (k) Gold
 - (l) Hair dyes
 - (m) Iodine
 - (n) Methylphenylethyl hydantoin (Mesantoin)
 - (o) Nitrogen mustard
 - (p) Pertussis vaccine
 - (q) Phenol
 - (r) Phenolphthalein
 - (s) Phosphorus
 - (t) Quinidine
 - (u) Quinine
 - (v) Snake venom
 - (w) Streptomycin
 - (x) Sulfa drugs
 - (y) Triethylenemelamine
 - (z) Trimethadione
 - (7) Physical factors
 - (a) Heat stroke
 - (b) Radiation
 - (c) Burns
- B. Thrombocytopenic purpura*
1. Primary
 - a. Senile
 - b. Purpura simplex
 - c. Hereditary hemorrhagic diathesis
 2. Secondary
 - a. Stasis—increased venous pressure
 - b. Traumatic or mechanical
 - c. Allergic or anaphylactoid
 - (1) Schoenlein-Henoch purpura
 - (2) Purpura fulminans
 - (3) Other
 - d. Skin diseases
 - e. Chemical agents
 - (1) Acetophenetidin (Phenacetin)
 - (2) Atropine
 - (3) Belladonna
 - (4) Bismuth
 - (5) Chloral hydrate
 - (6) Iodine
 - (7) Mercury
 - (8) Penicillin
 - (9) Quinine
 - (10) Salicylic acid
 - (11) Various anticoagulants
 - f. Systemic diseases and infections
 - (1) Nephritis
 - (2) Purpura fulminans
 - (3) Septicemia
 - (4) Enanthema
 - (5) Scarlet fever
 - (6) Other bacterial diseases
 - (7) Rickettsial diseases
 - (8) Viral diseases
 - g. Avitaminosis
 - (1) Scurvy
 - (2) Vitamin P deficiency
 - (3) Vitamin K deficiency
 - (4) Other vitamin deficiency
 - h. Cryoglobulinemia
- II. INCREASED PERMEABILITY OF VESSELS
- A. Allergic urticaria
 - B. Angioneurotic edema
 - C. Inflammation
 - D. Physical irritants
 1. Trauma
 2. Cold
 3. Heat
 - E. Serum sickness

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Situations which lead to changes in vascular patterns

AVERRILL A. LIEBOW

*Department of Pathology, Yale University School of Medicine,
New Haven, Connecticut*

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tissues. Masson (117) credits Berres (14) with their discovery in 1832 in erectile tissue where they were later described in considerable detail by Johannes Müller (123). The transparent wing of the bat provided an opportunity for observing the vessels in the living subject and here Paget (130) saw large arteriovenous anastomoses. Hyrtl (88) noted that when these structures were open there was pulsation of veins and arterialization of the blood within them. Sucquet (172) soon found precapillary arteriovenous connections to be widely distributed in man, but his results were discredited by such observers as Hoyer (80) and Berlinerblau (13) for the reason that they were based on injection of fluids of low viscosity. Arnold (4, 7) recognized the "coccygeal gland," which had been discovered by Luschka in 1859, to be analogous to the glomeruli caudales of animals and to represent in reality vascular complexes replete with arteriovenous anastomoses. He remarked on the muscular nature of some of the vessels. The first detailed histological description of the specialized transitional segment was by Hoyer (80) and this was elaborated by Grosser (65) in 1902. Max Clara (29, 30), author of the most extensive monographs on these structures, considered Schumacher (159) to be the discoverer of the epithelioid cells. The relationship of arteriovenous anastomoses to nerves was definitely demonstrated by Masson (116-118), and was subsequently investigated by Brown (25), and, with special reference to tumors, by Popoff (134).

Both normal and abnormal arteriovenous shunts can exert physiological effects, but these have been explored only in part. The observations of Grant (61)

AFTER WILLIAM HARVEY HAD DISCOVERED the circulation of the blood, there remained the mystery of its transfer from arteries to veins. A solution was provided by Marcello Malpighi in 1661 when he first saw the capillaries in the transparent lung of the frog (146). It took another half century before direct connections between an artery and vein (the spermatic), in this instance probably anomalous, were reported by Leali (43). Precapillary arteriovenous anastomoses are now known to exist normally in many organs and

on the intact rabbit's ear have been supplemented by a whole series of investigations by the Clarks (34, 36) who used a chamber technique. Recently, some attention has been paid to a possible secretory function of these structures.

Arteriovenous communications can be classified as:

A. "Normal" arteriovenous connections

1. Simple
2. Complex

B. "Abnormal"

1. Congenital
 - a. Familial
 - b. Isolated
2. Progressive acquired
 - a. Hemangiomatous
 - b. Within neoplasms
- c. Associated with disease, e.g., cutaneous spiders

C. Traumatic

D. Surgically induced

NORMALLY OCCURRING ARTERIOVENOUS CONNECTIONS

Structure

Connections between arteries and veins can range from simple bridges only slightly larger than capillaries (fig. 1) to complex channels with specialized cells in their walls (figs. 2 and 3). The former have been well described as components of the microcirculation by Zweifach (200). Both extremes can be encountered, for example in the rabbit's ear (148). Spanner, in particular, has emphasized the existence of transitional forms (165).

The more complex of these structures can be derived from a larger artery at a bifurcation, one division of which may be distributed to capillaries in the usual fashion. The other, or both, can become remarkably contorted and characteristically differentiated before joining a vein. In the intermediate or intercalated segment, called variously the Sucquet-Hoyer or Hoyer-Grosser canal, the wall becomes thickened by the presence of a broad layer of "epithelioid" cells which abut upon or partly replace the endothelium and appear to be differentiated from smooth muscle cells. At the beginning of the intercalated segment the epithelioid and muscle cells may be intermingled. When fully formed, however, the former approach a spherical shape and contain few or no myofibrils. Their cytoplasm is hyaline, or somewhat vacuolated, and gives no reaction for glycogen, fat, or mucin. A

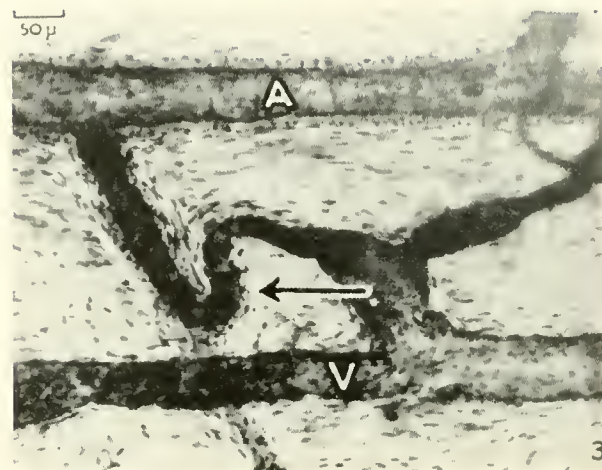


FIG. 1. A relatively direct arteriovenous anastomosis from the human ear. Specimen injected with Berlin blue, stained with hematoxylin and cleared. The arrow points to the terminal portion of the intercalated segment. There is a slight fusiform thickening nearer the arterial end of the latter, suggesting accumulation of muscle or epithelioid cells. [From Prichard & Daniel (135).]

circular layer of muscle fibers may or may not be preserved externally to the epithelioid cells. The elastic laminae usually disappear in the intermediate segment. The adventitia is a delicate collagenous reticulum supporting a very rich plexus of both medullated and nonmedullated nerves. The latter were well described by Masson (117, 118), and also in some of their finest details in the tongue of the dog by Brown (25). The latter noted thin unmyelinated fibers to terminate in the media and thick myelinated fibers (afferents?) with termination in the adventitia (fig. 3). Groups of such complicated arteriovenous anastomoses may be closely associated to form a "glomus" which may be enclosed within a dense connective tissue capsule.

Less complex arteriovenous anastomoses exist in which the intercalated segment is not tortuous. In some there is simply a well-developed inner layer of longitudinal muscle fibers without special epithelioid characteristics.

Distribution and Size

The distribution of arteriovenous shunts is now known to be almost universal. Aside from the glomus coccygeum, some of the largest and most complex glomera in man have been described in the skin and subcutaneous tissue on the flexor surfaces of the fingers and toes and in the nail beds. Their numbers have

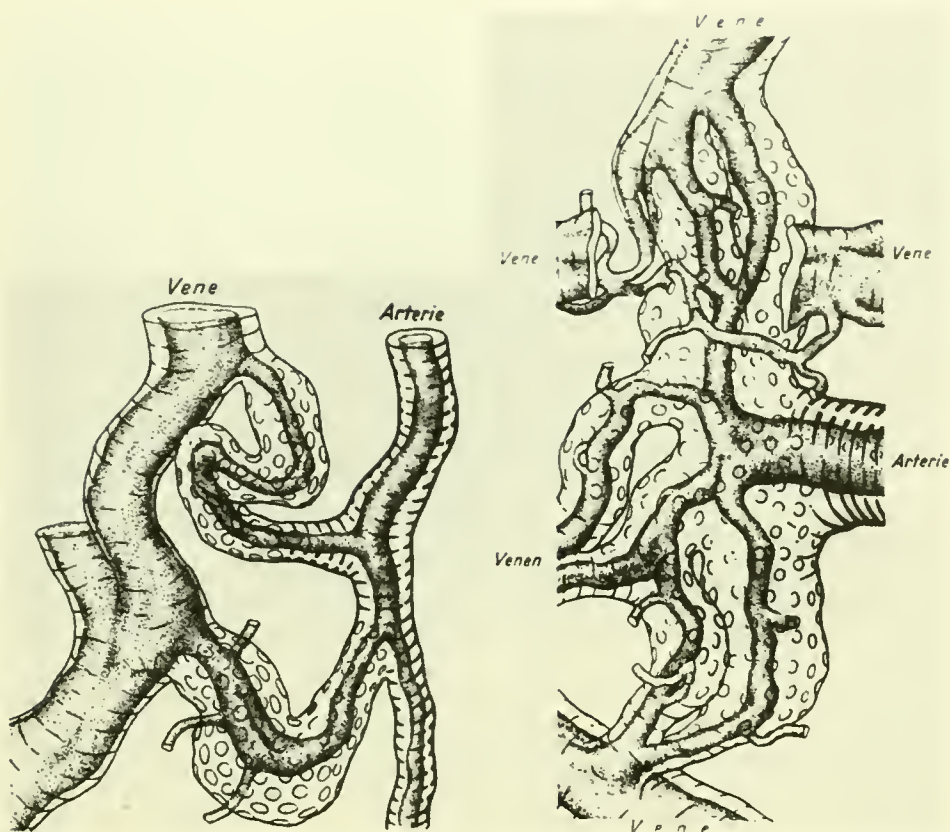


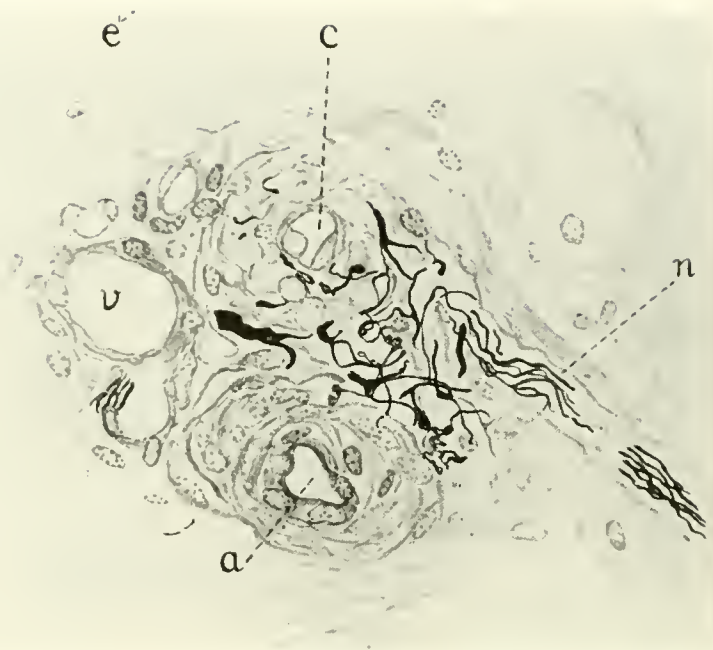
FIG. 2. Graphic reconstructions of arteriovenous anastomoses; relatively simple (left) and complex (right) communications. The accumulations of epithelioid cells are indicated. [From Staubesand & Genschow (168).]

been variously stated. For example, Grant & Bland (62) found 593 per cm^2 in the nail bed of the toe, and 293 per cm^2 on the plantar side, but Popoff (134) counted only 24 per cm^2 in the nail bed, and 18 on the ventral aspect of the same extremity. The latter considered only the more complicated glomera. Their size also varies: Grosser (65) found the external diameter to be between 55 and 85 μ in the nail bed, between 90 and 150 μ in the finger pad, and the internal diameter to be 18 to 22 and 10 to 30 μ , respectively. In the wings of bats the intermediate segment had an external diameter of from 90 to 280 μ , and an internal diameter of from 60 to 150 μ . The length of the junctional segment as measured in the tongue of the dog by Prichard & Daniel (136) was between 100 and 500 μ , usually between 200 and 300 μ .

Other locations where arteriovenous anastomoses have received detailed study include: erectile tissue, the ears in man (135); the nose, including skin, septum, and turbinates; and the gastrointestinal tract (8). Their existence in the kidney has been denied by

Trueta (178), and by Staubesand & Hammarsen (169), although Spanner (165) described them in the region of the sinus renalis, and Simkin *et al.* (162) found that spheres as large as 90 to 440 μ would pass from renal arteries to veins. In the lung, Weibel (186) could find no precapillary connections between pulmonary arteries and veins, but Prinzmetal *et al.* (137) found that glass spherules as large as 150 μ would pass from the former to the latter, and Parker *et al.* (131) observed that spheres of 75 to 80 μ would traverse the capillaries but those of 300 μ would not. Tobin & Zariquey (176) and Rahn *et al.* (140) have also concluded that pulmonary arteriovenous communications must exist normally. In perfused lobes Niden & Aviado (126) observed glass beads as large as 420 μ on the venous side in a perfusate introduced intra-arterially. Bostroem & Piiper (23), however, found that spheres of 28 to 36 μ would pass only exceptionally, and criticized the high pressures used by Tobin and his associates. Gordon *et al.* (60) also concluded from their own work, based on an appli-

FIG. 3. An arteriovenous anastomosis from the tongue of the dog. The richest nerve supply is to the intercalated segment. The filaments end in all levels of the wall, in which large rounded epithelioid cells predominate. Portions of a thick sensory fiber and sensory terminations are seen in the adventitia. [From Brown (25).]



cation of the principles of surface tension, that no connections larger than $25\ \mu$ were present in the lungs, intestines, or kidneys of rats and rabbits, in contrast with the extremities of these animals. Fritts and co-workers (55) stated on the basis of recently developed methods utilizing simultaneous T-1824 and radioactive krypton injections that if such shunts are functional they could account for not more than 1 per cent of total left cardiac output in normal human subjects. These problems have been judiciously reviewed by de Burgh Daly (41, 42) with special reference to possible influences of the nervous system. Connections between bronchial and pulmonary arteries are mentioned in the discussion of collateral circulation in this chapter.

Development and Fate

Arteriovenous shunts, at least those with a differentiated intercalated segment and complex "organoid" structure, do not exist in embryos. Popoff (134) could not find them in the extremities from 4.5 months of intrauterine life to term, although Clara (30) stated that they may be present in the newborn. After the age of 60 the complex cutaneous arteriovenous shunts tend to undergo atrophy and sclerosis.

Clark & Clark (36) observed the new formation of arteriovenous anastomoses in transparent chambers of the rabbit's ear where the tissue was induced to grow into an originally vacant space. Here the anastomoses were relatively straight, but were characterized by the

addition of an extraendothelial layer of differentiated cells. Stimuli leading to increase in blood flow seemed to increase the formation of these structures. Most of these shunts were temporary, and disappeared early or late, but some were permanent and had the property of contractility. This seemed to be associated with the development of nerves. Newly formed arteriovenous shunts were also found within 2 weeks after resecting a marginal segment of the rabbit's ear (148).

Function

With the disclosure of arteriovenous anastomoses in erectile tissue it became obvious that their functional state must vary from time to time. The ability of these structures to close was established in the living transilluminated rabbit's ear as early as 1930 by Grant (61). The use of the rabbit ear chambers with "preformed tissue" provided a clearer view in the hands of the Clarks (34), and they were able to make quantitative observations on the number, size, and rate of contraction of the anastomoses over intervals of many months. The specialized intercalated segments with their greater thickness and complex mural arrangements and rich nerve supply showed a faster and more complete contraction than the arteries, and the rhythm was independent of that of the latter. No explanation was apparent for the extremely variable responses of various arteriovenous anastomoses (fig. 4). The mechanism of closure has come under discussion and has been considered to be contraction of

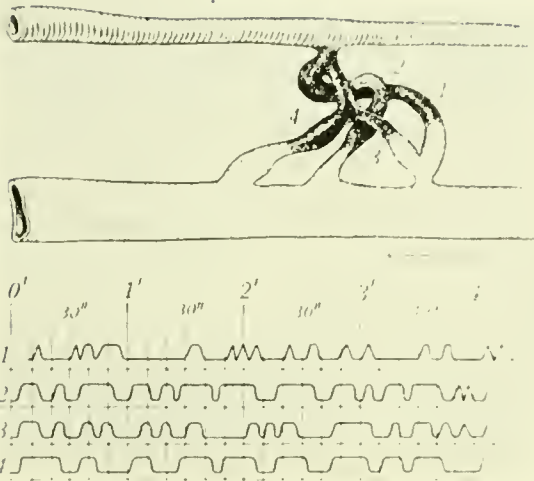


FIG. 4. A series of four arteriovenous communications from the rabbit's ear. The curves represent the rapid and uncoordinated rate of contraction or dilatation of each of these structures. [From Clark & Clark (34) as modified by Clara (29).]

an external layer of circular muscle in some instances, the accumulated epithelioid cells simply acting as a cushion that partly restricts the lumen even when the intercalated segment is open. In the absence of the circular muscle however it has been thought that closure is the result of swelling of the epithelioid cells, in consequence of a still unknown process. Benninghoff (12) was the first to suggest this idea, and Havlicek (71) called these cells "Quellzellen." Since these are approximately spherical, shortening, as with ordinary muscle fibers, is not possible. This mechanism has been extensively considered by Märk (112, 113).

Even direct observations have their limitations, since the functions of these structures may be multiple, and are not necessarily the same at all times, nor in all vascular beds in the same animal, nor in different species. There is now good evidence that they can respond both to neural and chemical stimuli, but there are numerous contradictions in details (119). It is of interest that so large a glomeroid structure as the coccygeal body can be removed, as in resection of the coccyx, without known physiological effects (160).

Local mechanical stimulation, such as rubbing, results in opening of the intercalated segments (34, 61). The effects of temperature appear to be determined in degree as well as direction by quantitative factors. Upon warming the whole animal both Grant and the Clarks found in rabbits a widening of the anastomoses. Moderate cooling was accompanied by their closure, and this was observed also in the paw of the dog by Bostroem & Schoedel (24). Sonomoto (163) also

found that the arteries and a majority of the arteriovenous anastomoses were constricted in the rabbit's ear during the winter. In the fingers of man, however, the anastomoses were closed by warming to an external temperature of 33 to 37 C, while cooling produced the opposite result. In the rabbit's ear Grant (61) found that cooling below 15 C produced an opening of the anastomoses, and that with greater or more prolonged reduction in temperature the arteries also became dilated, whereupon there was a rapid flow of blood through the anastomoses. He explained that this phenomenon kept the extremities from getting too cold. In human skin and in the feet of birds Grant & Bland (62) further established this function of the arteriovenous shunts by temperature measurements.

The consequences of anoxia were examined by Schroeder *et al.* (158) with plethysmographic methods, under the assumptions that the volume of an extremity kept at an initial pressure of 35 mm Hg will reflect changes in capillary pressure, and that of an extremity compressed at 15 mm Hg will reflect changes in venous pressure. They found that when the dog was breathing an atmosphere containing 8 to 9 per cent O_2 , the capillaries were wide without alteration in the functional state of the arteriovenous anastomoses, but when the oxygen concentration was between 6 per cent and 8 per cent the anastomoses became narrow without change in capillaries. In an atmosphere of between 5 per cent and 6 per cent O_2 , perfusion was slowed in consequence of constriction of the nutrient bed as well as of the shunts.

Stimulation of the cervical sympathetic was noted by Grant (61) to constrict the anastomoses as well as the small arteries in the rabbit's ear. The denervation of an extremity in the dog resulted in dilatation of the shunts (24). Folkow (54) stated that the cutaneous arteriovenous anastomoses become maximally dilated as soon as their constrictor fibers are cut, provided that there is no significant increase in hormone output of the adrenal medulla. Claude Bernard's classical observation that, when the peripheral end of the chorda tympani is stimulated, the rate of blood flow from the submaxillary vein becomes greater and the blood becomes bright red, has been interpreted to indicate the shunting of blood through the arteriovenous anastomoses (71). After vagotomy Curri *et al.* (40) reported that the arteriovenous anastomoses became widely open but lost reactivity to various stimuli.

The injection studies of Vastarini-Cresi (179) had suggested that, in general, vasoconstrictor substances

decreased and vasodilators increased the size of the arteriovenous connections. The vasoconstrictor effect of adrenaline was evident in direct observations of living vessels in rabbits' ears and it was found in the same preparations that histamine and acetylcholine dilated these shunts (61). This has been confirmed. According to Curri *et al.* (40) serotonin introduced intravenously in a dose of 8 mg resulted in a cessation of rhythmic activity of the intercalated segments.

Role in Bodily Economy

Surely one function of the arteriovenous shunts as a component of the microcirculation is concerned with regulation of regional blood flow, as exemplified in erectile tissue. In general, when the shunts are open the capillary bed may be largely or entirely bypassed, and total blood flow traversing the part may be maximally increased. This phenomenon, according to Grant (61, 62), helps to maintain the temperature of the extremity when exposed to extreme cold. Also it has been known since 1840, from the observation of Julius Robert Mayer, surgeon to the threemaster "Java," that venous blood tends to become "arterialized" in the tropics, indicating a dilated state of the arteriovenous connections (71). Thus, a thermoregulatory function has been suggested for these structures. Many of the arteriovenous anastomoses are however deeply situated, for example, in the periosteum or even within parenchymatous organs, and must have other than thermoregulatory functions. A third physiological role which has been considered, but which has not been truly demonstrated or tested experimentally, is in the regulation of blood pressure. It seems logical that if sufficient numbers of the direct arteriovenous anastomoses are widely open, systemic arterial blood pressure might fall.

It was suggested by Schumacher (160), largely on theoretical grounds, that the specialized epithelioid cells might have a secretory function—more specifically that they could secrete acetylcholine. Luckner & Staubesand (110) found in extracts of the coccygeal body a substance with the biological properties of acetylcholine in concentrations of 9000 μg per g. Indeed Schumacher (160) conceived that the pulsation of the arteriovenous anastomoses was a mechanism to maintain a level of the short-lived acetylcholine in the blood. This concept is of interest in that the epithelioid cells are rather widely distributed in small groups within the walls of arteries, for example at the vascular pole of the glomerulus, where they

had been described first by Ruyter (149) and later by Goormaghtigh (59).

Also rather theoretical is the idea that the connecting segments may be pressoreceptors, i.e., that the metabolism of the cells could be altered by variations in pressure, and that this effect could somehow be transmitted to the associated extensive neural plexuses.

Schumacher (160) thought that cells of the non-chromaffin paraganglia were analogous to the epithelioid cells of the intercalated segments, but there is no evidence that the carotid body is related to arteriovenous anastomoses, although some of these structures exist in its connective tissue capsule (1).

Clearly, there is much to be learned in the domain of function of the arteriovenous anastomoses. Further study doubtless will be highly rewarding.

ABNORMAL ARTERIOVENOUS COMMUNICATIONS

Arteriovenous connections of unusual size or location can occur as single or multiple lesions and, especially when multiple, can be familial (Osler-Weber-Rendu disease). The lesions vary from insignificant blue or purple spots on the skin or mucous membranes to complex cirroid masses with the arrangement of hemangiomas. These are important chiefly because they can bleed, as for example into the gastrointestinal tract.

In the lung, the pulmonary arteries and veins can come into free anastomosis with a right to left shunt. When of sufficient size, there are the expected consequences of desaturation of systemic arterial blood, cyanosis, polycythemia, clubbing, and at times thrombotic complications. Cardiac failure does not occur unless immense numbers of the arteriovenous fistulas are present (66). These can be of such small size as to be undetectable by angiography.

It was known to Virchow that acquired hemangiomas with a cavernous component also are the seat of arteriovenous communications, as indicated by the bright color of the effluent blood. Fistulation also can occur within certain neoplasms, especially when they become necrotic or hemorrhagic as in the case of chorionepithelioma. A bruit may then become audible over the lesion.

The "cutaneous arterial spider" has been recognized to consist in part of arteriovenous connections. The arterial component has in its walls specialized "glomus cells" (epithelioid cells), like other arteriovenous shunts. Such structures develop commonly in

association with severe chronic liver disease, in pregnancy, in persons with deficiency of the vitamin B complex, in the carcinoid syndrome, and also in certain apparently healthy individuals. The subject has been well reviewed by Bean (10).

TRAUMATIC OR SURGICALLY INDUCED ARTERIOVENOUS CONNECTIONS

The establishment of a connection of sufficient magnitude between an artery and vein may have major or even catastrophic consequences. These have been carefully worked out by experiment (76, 77, 79, 153).

The immediate effects upon opening the fistula are a fall in blood pressure, an increase in the heart rate and venous filling, and consequently a greater cardiac output. The regional veins become engorged. A thrill becomes palpable and a murmur audible over the fistula, and these can be abolished by exerting pressure over the vein proximal to the fistula. With a sufficiently large shunt, the total blood volume increases in course of time, and the blood becomes more dilute. Although initially the size of the heart and of the artery on both sides of the fistula becomes reduced, there is gradually a dilatation of the arteries and veins proximal to the fistula. The heart also becomes enlarged, chiefly because of dilatation. In late stages, the proximal artery may even become aneurysmally dilated (144).

Blood flow is toward the fistula, even from the distal artery. A large flow depends on a fistula which exceeds in size that of the proximal artery. Lewis (98) stated that the blood supply to the distal parts of the limb is at first diminished, but that with passage of time blood flow tends to become restored and may even exceed that to the normal limb. This results from the development of an extensive collateral circulation as will be discussed (fig. 5). Evidence for increase in the flow through the fistula is that cardiac dilatation and decompensation can occur late after the arteriovenous fistula is established. For the flow to increase progressively the distal artery must be distensible. Excessive scarring can interfere with this distensibility (79). Schenk *et al.* (153) made quantitative observations on the regional blood flow in all limbs of experimental arteriovenous fistulas using a square wave electromagnetic flowmeter. They found that in the femoral fistulas in dogs, flow tended to increase and at the end of approximately 1 year had



FIG. 5. Traumatic arteriovenous fistula. The trauma occurred accidentally during attempted biopsy of lymph nodes from the anterior scalene region in a 72-year-old man. Several weeks later the patient noted pain and a pulsatile swelling in the region of the wound over which a systolic bruit was audible. The specimen is a vinylite cast of the arteriovenous fistula showing numerous tortuous arterial channels related to the fistula.

not yet reached stability. In contrast with the femoral fistulas, flow through the proximal artery of carotid-jugular fistulas tended to diminish with passage of time, but in both types of fistulas there was a marked increase in flow through both the arterial and venous distal limbs.

COLLATERAL CIRCULATION

Collateral circulation may be defined as blood flow that pursues a channel or system of vessels which is alternative to or develops in substitution for a major vascular pathway. To understand collateral circulation would require not only a complete knowledge of the mechanisms of angiogenesis, and therefore of all growth, but also of the anatomical and functional responses of blood vessels in general. At the present writing only limited answers can be supplied to such questions as: What starts the growth of collateral vessels and what controls the rate of their increase; what stops them from expanding indefinitely; when newly formed, what guides them to their proper place; what determines the structure of their walls.

Some two hundred years ago the great John Hunter was amazed to find that not only did the growth of the stag's antler proceed uninterrupted when its

major nutrient artery was ligated, but that in time there was a prodigious growth of new vessels (146). He was not the first to observe this providential activity of nature, since Antyllus, a pioneer in the surgical treatment of aneurysms fifteen centuries before him, had noted that interruption of the artery to a limb does not necessarily result in its loss (97). Morgagni also had anticipated Hunter in observing collateral vessels. After numerous experiments Hunter could conclude only that "vessels go where they are needed" (124).

In attempting in this chapter a précis of some major advances in the understanding of this complex subject a sense of wonder and frustration still remains. Scholarly reviews have been published by Mulvihill & Harvey (124), Quiring (139), Longland (108), Learmonth (96) and Rau & Schoop (141) among others. Here it will be necessary to consider chiefly what is known of general principles, and little consideration can be given to specific collateral beds. To the coronary circulation detailed consideration has been given by Spalteholz (164), Gross (64), Gregg (63), Schlesinger (155), and very recently by Blumgart (21), Pepler & Meyer (133) and Laurie & Woods (95). The pulmonary collaterals have been investigated by Miller (121) Berry & Daly (15), Verloop (180, 181), State *et al.* (166, 167), Parker & Smith (132), Tobin (175), Töndury & Weibel (177) and by Liebow *et al.* (101, 103) among others. A recent study of hepatic collateral circulation has been published by Hales *et al.* (68).

Some Aspects of Angiogenesis in General

A brief review of the painstaking observations upon angiogenesis by such devoted students as Golubew (58), Thoma (174), Evans (48, 49), Sabin (150), Hughes (81, 82), and the Clarks (31-37) might well serve as a guide to approaching the problems of the developing collateral circulation.

In embryos there is an initial phase of primary differentiation of vessels from connective tissue cells, and a later stage of extension and elaboration. The latter occurs from endothelium of vessels already formed by a process of "sprouting," and comes largely if not entirely to replace the former. Certainly most of the vascularization of the developing organs of the embryo, such as the limb buds of birds, occurs by ingrowth of sprouts and not by formation *de novo* of vessels within the tissue (48, 49, 150). As early as 1869 Golubew (58) observed in the transparent tail

of the living tadpole that the capillary sprouts were at first solid but then developed a lumen by a process of "hollowing out" beginning proximally as vacuolation. The development of new capillaries by sprouting was further studied soon thereafter by Arnold (5, 6). E. R. Clark (31) in the same subject noted atrophy of certain newly formed capillaries. Aeby's (2) concept that the anlage of the entire vascular system was represented by capillaries in retiform arrangement received strong support from the study of injected and serially sectioned embryos by Evans (48).

It has been established that vessels destined to become major conduits for blood in the adult can differentiate to a limited but recognizable degree even in the absence of circulating blood. This was known to such early embryologists as Baer and His, and was studied in greater detail by Sabin (150). Experimental support was provided by Loeb (107), who stopped the heartbeat in fundulus larvae chemically, and later by Chapman (28) when he removed the heart in chick embryos. The aorta and certain other main arteries and veins nevertheless become recognizable. Presumably, this limited self-differentiation of the vascular system is determined by hereditary factors.

Thoma (174), long a student of responses of the vascular system, understood these influences, but to him is due the credit of recognizing the molding force of the circulating blood. He observed, during the first 3 days of development of the area vasculosa of the chick, that certain pathways of most rapid blood flow increased in caliber and length and thereby acquired the characteristics of magistral vessels, while others underwent diminution and atrophy. He codified the principles of what he termed histodynamics: *a)* The growth of the lumen of a vessel, that is the increase in surface of the wall, depends upon the rate of blood flow. *b)* The growth in thickness is dependent upon the tension in the wall, which in turn is related to the diameter of the vessel and to the blood pressure. *c)* It is an increase in blood pressure above a certain level, which limit is defined by the metabolism of the particular tissue, that determines the new formation of capillaries. The formulation of the principles, although they have not been universally accepted in toto, has stimulated much thought. The factor causing enlargement of an artery was, for example, thought by Clark (31) to be the amount of blood flow rather than the rate as suggested by Thoma (174). Clark proposed the hypothesis that when the chemical interchange through the wall of

a capillary exceeds a certain level, a sprout is sent out. If on the contrary there is a diminution below a critical point, there results a decrease in the caliber.

Hughes (82) in 1937 for the first time supplied measurements of the actual rate of blood flow and was able to substantiate Thoma's first principle, when he found a relationship between the diameter of an artery and the rate of blood flow in the area vasculosa of the chick. He had found that the first differentiation of the vitelline artery was mainly effected by the disappearance of connections with smaller vessels to either side (81). As the vessel increased in diameter the endothelial cells, and their nuclei, became elongated at right angles to the axis of the vessel. Mitosis then occurred. By counting and measurement Hughes (82) was later able to establish that increase in cells is proportionate to increase in area. He admitted however that some of these cells might represent incorporated mesenchymal elements, rather than the products of division of earlier endothelial cells, especially in veins.

The development of the transparent chamber method made it possible to explore under direct vision to what extent angiogenesis in the adult would recapitulate ontogeny. Ziegler (196) first introduced glass chambers for studying the genesis of tubercles, but these were buried in muscle or subcutaneous tissue. Sandison (152), at the suggestion of E. R. Clark, made transillumination possible by bringing the chamber to the surface. This enabled an intimate and continuous observation of vessels in process of formation in adult animals. Sprout formation, fusion of adjacent sprouts, the development of lumina in newly formed capillaries, atrophy of some capillaries, and the differentiation of others into arterial and venous vessels, were all observed in transparent chambers in the ears of rabbits by Sandison (152) and the Clarks (33, 35), and in similar chambers in dogs (122). For a further discussion of the transparent chamber technique see Chapter 27.

Williams (190), in autografts of subcutaneous tissue to previously vascularized rabbit ear chambers, found that new vessels can be formed by lateral sacculation or "herniation" of the endothelial wall as well as by canalization of sprouts. Such adjacent branches can fuse to give rise to new connecting channels. He recorded also the development of arteriovenous anastomoses. In previous work with omental autografts he observed the formation of connections between host and graft vessels, in some instances within 48 hours (191). It was astonishing to note the

reconstitution of some of the original vessels within separate fragments of the grafts, and that this could take place before blood flow began. He considered that the principal stimulus to endothelial proliferation was probably hypoxia of a certain degree and duration (190). Under conditions where hypoxia was unquestionably present and maintained for more than 3 days, vascular proliferation was extreme. When free blood flow was established rapidly, however, plexus formation was inhibited. In similar chambers within dorsal skin flaps of mice Merwin & Algire (120) found that the original vascular channels in grafts of thyroid tissue survived and were the active structures in establishing connections with host vessels. Grafts of tumor tissue, however, were quickly provided with a rich vascular network derived from the host. Solid sprouts of the host vessels can grow against the "grain" of connective tissue, while ordinary vessels of the graft are oriented parallel to the cells and fibers of the connective tissue.

The Clarks (32) found in rabbit ear chambers that arteries can be developed without acquiring a nerve supply, and that these do not contract spontaneously but react passively. They can, however, respond to chemical stimuli.

Types of Collaterals

Collateral vessels may be preformed, or newly formed, but it may be difficult to distinguish the two. Weyrauch & De Garis (189), after ligation of sufficient original arteries and veins in the mesentery, considered some vessels newly formed on the basis of vastly increased numbers and unusual position. It may be questioned, however, whether such vessels were not developed from smaller arterial or venous channels. Under some circumstances, as for example in vascular channels traversing a former serous cavity, there can be no doubt of their new formation.

In discussing pre-existing collaterals a convenient terminology has been devised by Longland (108) according to their ultimate function. The plexus of connected arteries that may span an obstructed portion of a major artery he has called the "midzone," the main artery proximal to the midzone, the "stem," and the distal, he has termed the "re-entrant" (fig. 6). His measurements showed that in the extremities of the rabbit, at least during the first 16 weeks, the vessels in the midzones grow relatively more than the stem or re-entrant vessels (fig. 7).

Learmonth (96) has described two types of col-

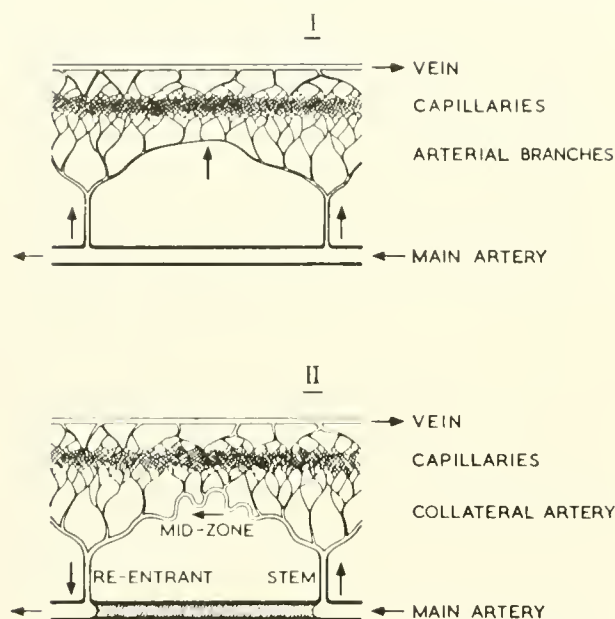


FIG. 6. Longland's (108) concept of the stem and re-entrant vessels and midzone in a collateral circulation after occlusion of an artery.

lateral circulations: In the first type, after a short course in alternative channels, the arterial blood is returned into the main artery or arteries of the part. In the second type blood reaches the part beyond an obstruction via terminal branches only; here the pressure is low and quantity probably reduced. In duodenal transplants, North *et al.* (128) found that in some instances only numerous fine extramesenteric vascular connections had formed, while in others the connecting channels were quite large.

Forces Affecting the Development of Collateral Circulation

In the general consideration of angiogenesis there emerged at least three significant types of influences: hereditary, mechanical, and chemical; moreover, the responses of vessels once formed are governed also by the action of nerves. These same forces affect collateral vessels. Their immediate responses must be considered separately from late responses.

MECHANICAL FACTORS. The fall in pressure peripheral to the interruption of a major artery may have mechanical or chemical effects that could stimulate the development of collateral circulation. The idea of a chemical mechanism, especially anoxic, was strongly championed by Sir Thomas Lewis (98). The one does not necessarily exclude the other.

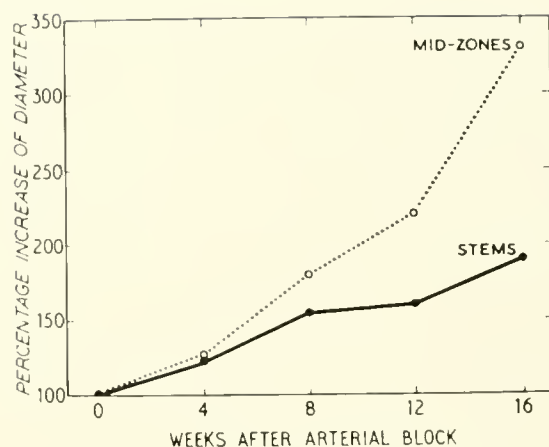


FIG. 7. Mean growth rates of stems and midzones (% increase per month of initial diameter [= 100%]). The relatively greater growth of the midzone as compared with the stem vessels in a collateral system as established from measurement of angiograms. Data from 7 rabbits. [From Longland (108).]

Many attempts have been made to assess the relative impact of the two.

Winblad and associates (192) measured both pressure and pO_2 in an extremity of the dog in which the superficial femoral artery was acutely occluded. There was a quick drop in pressure to between 35 and 60 mm Hg. After 4 min the pressure level remained constant, with the systolic pressure exceeding the diastolic before occlusion (fig. 8). Widening of the collateral vessels was demonstrated angiographically. The pO_2 of the tissue fell only very slightly, and rose again to control values within 5 to 8 min. The rate of recovery was not affected, whether the artery distal to occlusion was perfused with highly oxygenated or venous blood by means of an artificial pumping system. Similar experiments were performed by John & Warren (90) with like conclusions. The rapid appearance of the collateral vessels was also demonstrated angiographically, as was their quick regression when continuity of the main artery was restored. These observations suggest the relative importance of mechanical factors. Völpel (184) found that with repeated interruption of the femoral artery the blood pressure in the distal segment would rise more rapidly. By creating a shunt between the left femoral artery and right femoral vein, and interrupting the left femoral artery below the arteriovenous connections, collaterals did not develop; but if the shunt were interrupted they quickly reappeared. However, in the distribution of the right femoral artery the collaterals became visible upon its occlusion as in the absence of a shunt. Further, if the distal

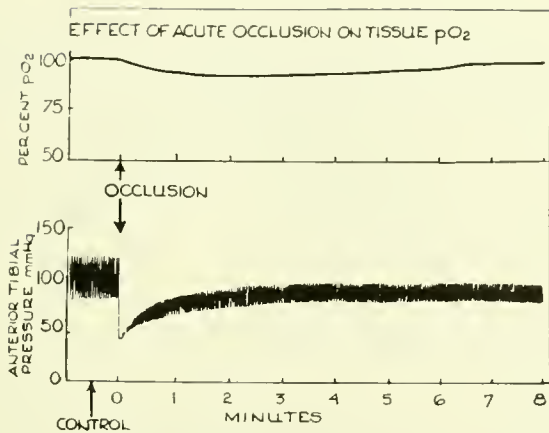


FIG. 8. Pressure and oxygen tension in the lower extremity of a dog immediately after occlusion of the superficial femoral artery. The pressure in the anterior tibial artery falls, but within 3-4 min rises to a plateau below the initial level which is thereafter maintained. The tissue pO₂ drops only slightly and temporarily. [From Winblad *et al.* (192).]

portion of a right femoral artery were connected by catheter to the left femoral artery, so placed that the catheter lay in the region of re-entry of collaterals and obstructed these, the collateral vessels nevertheless expanded. Schoop & Jahn (157) stress that, for the later development of collaterals, flow is rather more important than differential pressure.

The appearance of alternative arterial channels to peripheral capillary beds is well exemplified in coarctation of the aorta, where collateral circulation was studied centuries ago.

Valuable insights into the mechanisms governing the development of collateral circulation have come from the thorough and long-continued observations of peripheral arteriovenous fistulas, both clinical and experimental, by many observers. As early as 1756 and again in 1761 William Hunter published on this subject and noted the appearance of a collateral circulation in relation to the fistulas (84, 85). Mont Reid (144) and Emile Holman (77, 79), in particular, contributed important information. Holman's major point is that as soon as these fistulas open, there is a fall of pressure in the arterial segment distal to the fistula, as indicated by the cephalad flow of blood within it. The peripheral resistance to onflow of blood in smaller arteries circumventing the fistula is therefore reduced, whereupon these vessels begin to carry more blood. If the artery distal to the fistula is ligated or even if its lumen is reduced to one-half by means of a constricting aluminum band, the collateral circulation is relatively meager. The most telling experiment

against the idea of "tissue need," as a determinant of the expansion of the collateral arteries, is that amputation of the extremity does not reduce the extent of the collateral circulation associated with an arteriovenous fistula. It appears that the effect of the fistula in stimulating a collateral circulation is greater than simple ligation of the artery to a limb.

Deterling *et al.* (44), however, cautioned that the abundant collateral circulation related to an arteriovenous fistula may be to a great extent spurious, being rather an enormously dilated plexus of veins that does not function as collateral circulation after obliteration of the fistula. If the arteriovenous fistula is excised, the collateral, according to these observers, is usually no greater than that of controls after simple ligation of the artery. They also observed that sympathectomy tends to insure a greater collateral.

A closer definition of conditions at an arteriovenous fistula has been given by Holman & Taylor (79). The development of a large collateral circulation was stated to depend on the existence of a fistula larger than the proximal artery and also on the presence of a widely patent artery distal to the fistula. Flow through the fistula can increase progressively, provided that the proximal artery and vein remain distensible. Sir Thomas Lewis (98) presented evidence, based on calorimetry, that the blood flow to a leg that had been the seat of an arteriovenous fistula for 18 years was actually greater than that of the normal side.

Because of its double blood supply, the lung offers a useful stage upon which various factors controlling collateral circulation can be analyzed. Expansion of this circulation can occur under various circumstances of disease. Moreover, it can easily be induced experimentally and measured with considerable accuracy, at various stages, by application of bronchspirometry and blood gas analysis, or by use of dye distribution techniques. Finally, it is possible to distinguish with confidence certain collaterals as newly formed rather than preformed.

The relative pressures and flows in the pulmonary and bronchial arteries have been measured and an increase in aortic pressure has been found to augment inflow from the latter (15, 26, 151).

When the main pulmonary artery to one lung is ligated in the dog, expansion of the collateral circulation continues for at least 18 months (20). The mechanism is only partly understood, but its major features appear to be as follows:

Under ordinary circumstances in the normal lung the bronchial and pulmonary arterial circulations

meet predominantly, if not exclusively, as capillaries in the region of the alveolar ducts (121). The distal ramifications of the pulmonary artery supply the alveoli; the bronchial arterial distribution is to the substance of the bronchi, vessels, and interstitial tissue. There are at least two forces that tend to prevent the onflow of blood within the terminal bronchial arterial radicals to the alveoli. The first of these is the frictional resistance offered by the narrow vessels; the second is the counterpressure transmitted from the terminal branches of the pulmonary artery. With interruption of the major pulmonary artery the second of these forces is abrogated, whereupon further onflow of blood takes place in the bronchial vessels. As the flow increases in these vessels they become larger, by mechanisms still largely mysterious. Thus there is increasing access to the low resistance capillary bed of the lung. The course of the blood flow is from the aorta through the bronchial arteries to the pulmonary capillaries, pulmonary veins, and left atrium. This represents a left-to-left recirculation of blood. The flow increases from an initial value of less than 25 ml per m² per min to volumes in excess of 1 liter per m² per min in a period of approximately 18 months. In many respects this shunt is analogous to an arteriovenous fistula between the aorta and left atrium (109). As in the case of peripheral arteriovenous fistula, increase in flow is continuous for very long periods. Furthermore, the flow is many times in excess of the "need" of the tissue, evidence that it is induced primarily by the mechanical effect of the low peripheral resistance introduced into the systemic arterial circuit. Collateral flows of considerable magnitude have also been found in the lungs of patients in whom pulmonary arteries had been ligated because of operative misadventure (52, 56).

Great anatomical enlargement of the bronchial arteries occurs in such congenital lesions of the heart and great vessels as result in a low pulmonary arterial pressure, i.e., tricuspid or pulmonic atresia, or stenosis and tetralogy of Fallot. The collateral circulation tends to be greatest where there is a right to left shunt with polycythemia and a consequently greater tendency to further obstruction of pulmonary arteries by thrombosis. Bing and his co-workers (19) were pioneers in attempting measurements of the collateral blood flow in these conditions, although their methods were subject to certain errors. In a series of 38 patients with tetralogy they found collateral flows to exceed 500 ml per m² per min in 26 patients, 1 liter per m² per min in 16, and 1.5 liter per m² per min in 8.

The problem of the genesis of the collateral circulation is perhaps simpler on the venous side. The major pulmonary veins and the true bronchial veins that drain into the azygos venous system and right side of the heart are always connected by short pre-capillary stems (199). With occlusion of a major pulmonary vein near the hilum the pressure within it increases, and with this the *vis a tergo* forcing blood into the connected bronchial venous stems becomes greater. Consequently, blood flow in the stems increases and again they become remarkably enlarged (86, 87). Here flow becomes greater not because peripheral resistance is reduced but because pressure at the source is increased. The moment of force again is mechanical, however. Numerous analogues exist in the systemic venous circulation.

NEURAL FACTORS. There is evidence that the nervous system can exert a control both on the immediate and even late development of collateral circulation. At least in part this is related to its influence on the musculature of vessels.

As early as 1876 Latschenberger & Dealina (94) observed that sectioning of the major nerves of the thigh in experimental animals prevented collapse of the segment of femoral artery distal to the point of clamping beneath Poupart's ligament; thus the blood pressure did not drop when the artery was opened, as it usually did in the presence of intact nerves. Stefani (170) found that denervation of an extremity in the salamander was associated with gangrene upon ligation of the axillary artery, while neither the ligation itself nor denervation alone produced this untoward result. Nothnagel (129), however, observed that a much greater collateral circulation developed in a period of 8 weeks in an extremity of the rabbit after ligation of the femoral artery when the sciatic and crural nerves had also been transected than when the nerves were intact. He also noted that the more expanded vessels were structurally altered in that they contained more muscle (fig. 9).

That it was the influence of the sympathetic nervous system specifically that accounted for this observation was suggested by Ferris & Harvey (50), who recorded a sudden rise in the temperature of the dog's extremity some 4 hours after ligation of the femoral artery. That this was the result of a reflex vasodilatation was previously inferred from Halsted's (69) observation of a remarkable increase in the temperature of the upper extremity of a man following a resection of a large subclavian aneurysm and ligation of the left subclavian and axillary arteries. Halsted

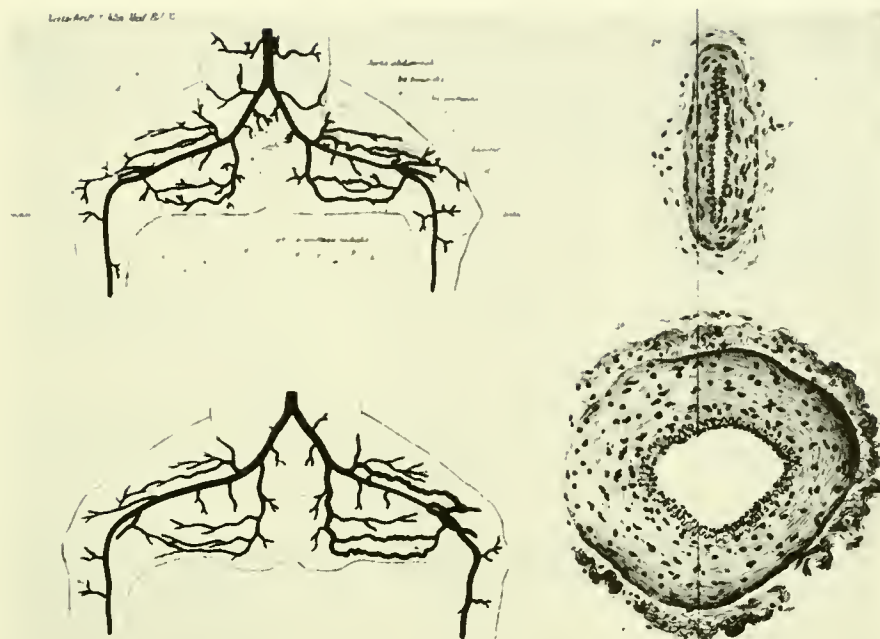


FIG. 9. Effect of denervation upon collateral circulation. In the upper half of the drawing is shown the collateral circulation 22 days after interruption of the left femoral artery in a rabbit. In the lower half the more extensive collateral circulation in a comparable preparation but with the crural and sciatic nerves cut at the time of the arterial ligation. At the right above is shown a section of the profunda femoris on the control side, and, below, a comparable section after function for 8 weeks as a collateral vessel following ligation of the femoral artery. There is hyperplasia as well as hypertrophy of the muscle. [From Nothnagel (129).]

had become intrigued by Lériché's studies of the periarterial sympathetic nerves. Mulvihill & Harvey (125) found that with sympathectomy the temperature of an extremity did not fall after ligation of the external iliac artery (fig. 10). Theis (173) and later Longland (108) confirmed this observation by various methods. Both indicated the persistence of the effect over several months. Injection with alcohol of the main artery beyond a ligation in the anterior extremity of the dog, a procedure that was presumed to produce a destruction of the sympathetic nerves within it, seemed to result in a better development of collateral circulation than in the leg of the control side (91, 92).

Turning to the "microcirculation," Fulton *et al.* (57) provide a description of several orders of nerve plexuses related to the small vessels in the cheek pouch of the hamster. The networks are sufficiently rich to innervate all the smooth muscle cells of the vessels. The development of a complement of non-medullated nerve fibers in newly formed arterioles in chamber preparation of the rabbit's ear has been demonstrated by the Clarks (37). They have established that only vessels supplied with such fibers are capable of spontaneous contraction. The bearing of these observations on the development of collateral circulation remains for further exploration.

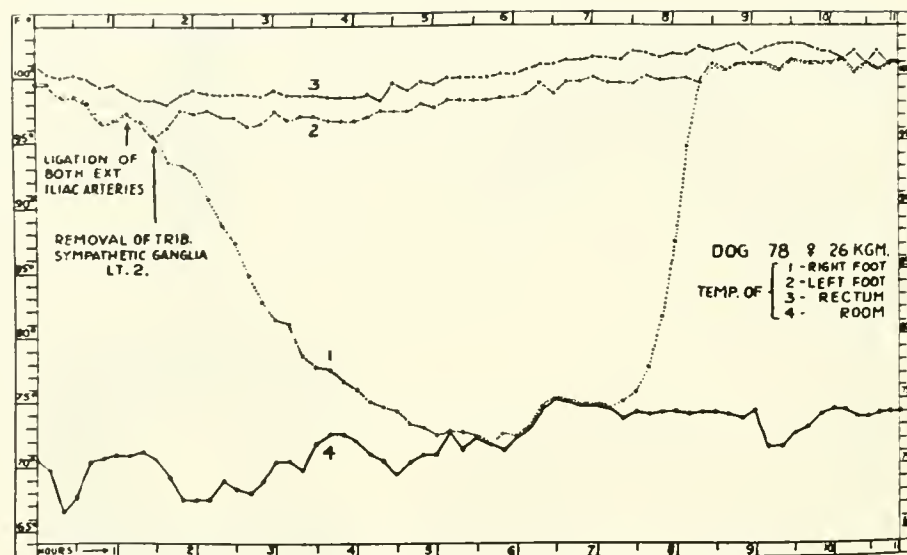
In 1958, North & Sanders (127) reported that the innervation of the mouse ear seemed to have no effect on the growth of collateral vessels.

The existence of a "basal vascular tone" of local muscular rather than neural origin has been considered by Folkow (53, 54). Evidence for an apparently nonneural dilator response, probably transmitted by the musculature of the vessel itself, has been adduced by Hilton (75). He found that cocainization of a femoral artery feeding actively contracting muscle abolished its dilatation, while cutting the nerve to the extremity and curarizing the animal did not. This dilator response traveled up the artery at a slow rate, of the order of 10 cm per sec. Such phenomena may have a bearing on the total problem of the reaction of collaterals.

When the influence of the nervous system, and possibly also of intrinsic myogenic influences, is considered, it is clear that the important effect relative to collateral circulation is the lysis of vascular tone. This is expressed essentially in the alteration of mechanical forces. Possible influences on the growth of vessels are as yet unknown.

CHEMICAL FACTORS. There are at least four ways in which chemical substance could affect collateral circulation: 1) By regulating vasodilatation. 2) By controlling the proliferation of new vessels. 3) By stimulating and inhibiting the growth of vessels. (Growth itself is obviously a chemical process, although it could be initiated by mechanical or chemical factors.) 4) By guiding vessels to specific destinations.

FIG. 10. Effect of left sympathectomy upon temperature of an extremity after bilateral ligation of iliac artery. On the side of sympathectomy the temperature is maintained. On the opposite side it falls gradually to room temperature but rises with great rapidity at about the 8th hour following the ligation. [From Mulvihill & Harvey (125).]



The idea that metabolites formed locally in anoxic tissue can produce vasodilatation received early experimental support. Marey (115) had observed that hyperemia occurred in the arm after a sufficient degree of compression either by mercury (150–200 mm Hg) or in a pneumatic chamber. That this did not require participation of the central nervous system and that it was not the result of squeezing the nerve itself was demonstrated by Bier (17, 18), who noted reactive hyperemia after clamping and then releasing the artery in the limb of a pig severed from all connections with the body except for the major vessels; compression of the nerve in another preparation produced no such effect. John & Warren (90) showed that an increased flow was associated with reactive hyperemia. Possible sources of error in interpretation are that nerves intimately associated with the arteries, or axone reflexes, might be involved, or that a local myogenic conducting mechanism might exist. Bier explained enlargement of the major arteries on the basis of decrease in peripheral resistance of the capillary bed.

Controversy regarding chemical mechanisms in collateral circulation was further stimulated by Thomas Lewis's (98) dictum "—and we are brought to ask if arterial growth is not directly controlled by a stimulant, a chemical stimulant arising locally as a product of tissue need and acting locally." If this had no other good effect, it at least inspired a vigorous investigation of the mechanisms of collateral circulation, especially those related to arteriovenous fistula. The primacy of mechanical over chemical phe-

nomena, under some circumstances when both might be operative, was suggested in the case of the extremity after ligation of a major artery by Winblad *et al.* (192), and by John & Warren (90), among others, and in the case of arteriovenous fistula by Holman (77) in his amputation experiment.

Certain factors, such as anemia, exercise, and decreased arterial pO_2 , can increase interarterial anastomoses at least in the coronary system (45, 46, 197, 198). Just how this is brought about is not known.

The Clarks (33) had observed that the same growth conditions which favored the formation of new blood vessels also stimulated the growth of other tissues in the same region. They were led to suggest: "As for the chemical substance or substances which may stimulate the formation of new capillaries, they should be sought in embryonic tissue and in inflammatory exudates, since it is in such environments that active vascular formation takes place." In autografts of connective tissue in transparent chambers Williams (190) concluded that hypoxia of a certain degree is a stimulus for growth of vascular endothelium. No specific data are given, however, to support this statement.

For the growth of vessels, Nothnagel (129) offered a deceptively simple explanation: "Anemia of peripheral parts results in an increased flow through collaterals, whereupon there is an augmented nourishment of the walls of these vessels, by the materials with which they become increasingly perfused." To substantiate this idea it is necessary to demonstrate

that substances transported through the lumen of a vessel serve to nourish it, or that after the flow becomes greater both nourishment and growth increase.

Compelling evidence does exist that chemical factors affect the growth of vessels in general, and the development of collateral circulation in particular. This becomes especially clear in organs with a double blood supply such as the lung. For example, there is general agreement that the actively metabolizing cells of primary malignant pulmonary neoplasms receive their blood supply from systemic vessels (39, 99, 194, 195). This would indicate the effect of chemical rather than mechanical factors, since the vast majority of the pulmonary capillaries represent a bed supplied by the pulmonary artery. In fact, with the growth of tumors the pulmonary arteries and veins tend to be obstructed or peripherally displaced. This may have some practical importance, since attempts have been made to subject pulmonary neoplasms to high concentrations of cytotoxic agents by injecting them into the pulmonary arteries leading to the involved segments. There is disagreement on the blood supply of metastatic tumors, since some (99) have found them likewise to be vascularized from the aorta, while others (39) concluded that the bronchial arteries did not nourish the metastatic tumors. Possibly the disagreement indicates variation in the blood supply. In the case of the liver, according to Hales (personal communication), both primary and metastatic tumors are supplied by the hepatic arteries.

Other newly formed tissues in the lung also are nourished by systemic arteries. Again this implies that chemical factors must be at work. Thus, in organizing pulmonary disease, as in bronchiectasis, the granulation tissue is derived at least in large part from the bronchial arteries (104, 194). Ultimately precapillary anastomoses are formed with branches of the pulmonary arteries. That this is not necessarily the outcome of enlargement of existing precapillary anastomoses, is indicated by the observation that vessels penetrating into the lung from intercostal arteries via adhesions anastomose with pulmonary arteries in similar fashion (102).

The peculiar "tropism" exhibited by newly formed collaterals in the lung must also have a chemical explanation. It is well established that ligation of the pulmonary artery induces expansion only of arterial collaterals (102). After interruption of the pulmonary veins, only the venous collaterals expand (86). Proliferating branches of intercostal vessels that enter the

lung through the pleura are of the same type, arterial or venous, depending on the stimulus, and the arteries form precapillary connections only with arteries, and the veins only with veins. When both major limbs of the pulmonary circulation are interrupted, the expansion of both collateral systems is induced, and both types of collaterals penetrate inward through pleural adhesions (183). These collaterals must be newly formed, from capillaries in granulation tissue which did not exist previously but which comes to obliterate the pleural space after the operative manipulation. Remarkably, again the transpleural branches of the intercostal arteries establish precapillary connections only with the pulmonary arteries, and the intercostal veins connect likewise only with pulmonary veins. If these were mechanically induced there should be "short circuits" between the intercostal arteries and veins, since they share a common capillary bed in the granulation tissue as it is first formed, and the greatest pressure gradient under the circumstances is obviously from intercostal arteries to intercostal veins. Yet such short circuits have rarely if ever been observed. Rather, the blood pursues the longest course, from the intercostal arteries through precapillary anastomoses into the pulmonary arteries, to the pulmonary capillaries, to pulmonary veins, and finally through precapillary connections into the collateral veins. The chemical factors that must be responsible for this are still unknown.

There is some suggestive, but as yet imperfect, evidence that hormones can exert an influence on the development of collateral circulation. The collateral circulation that develops within a few months after ligation of a pulmonary artery in puppies less than 48 hours old seems immensely greater by gross inspection than that appearing after a comparable interval of time in adult animals after the same procedure (105). The results of a study of the effect of hormones on collateral circulation after interruption of the iliac artery in rats were, however, equivocal (147). Cortisone seemed to inhibit the collateral circulation, just as it did the connective tissue proliferation in the region of the lower abdominal incision where, as a result, hernias appeared. The weight increase of these animals, however, stopped when cortisone was administered. It might be expected at the end of the experiment that the smaller animals would have smaller vessels. This problem, however, should be reinvestigated.

Studies of the earliest phases of development of the

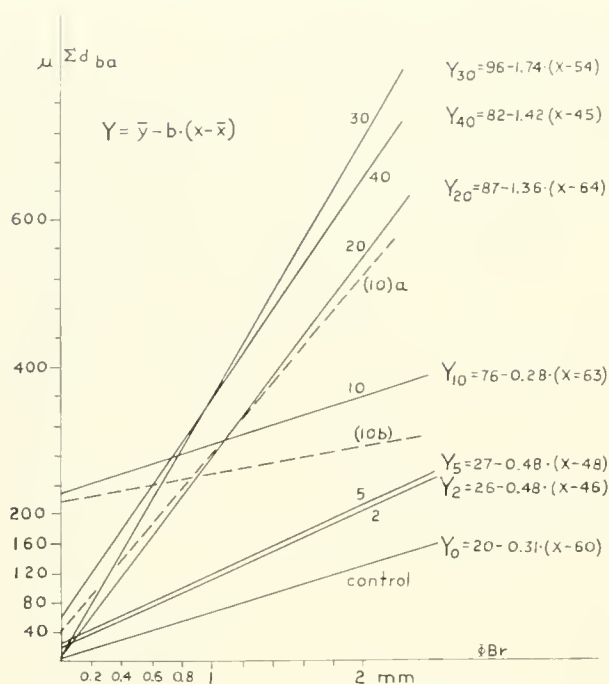


FIG. 11. Trend lines of curves showing relation of diameters of bronchial arteries (*ordinate*) to bronchi and bronchioles which they accompany (*abscissa*), as calculated from observations in individual rats. Between the 5th and 10th days there is a sudden increase in slope. This corresponds in time to the onset of proliferative activity in the walls of the collateral vessels. [From Weibel (188).]

collateral circulation after interruption of the left pulmonary artery in the rat also provide information on mechanisms (188). The process appears to be biphasic, with initial mechanical expansion, followed by active proliferation of vessels. This is reflected in quantitative observations on the size of bronchial arteries as related to the bronchioles which they accompany. In the first phase the arteries increase in diameter, but the ratios to the diameters of the bronchioles have approximately the same slope, suggesting simple mechanical expansion (fig. 11). Between the fifth and tenth days, the slope suddenly becomes much more steep. Histologically, at about the fifth day mitoses begin to appear in large numbers both in endothelial and muscle cells, indicating that active proliferation is in progress. The new cells appear as solid sprouts that seem to extend to their destinations in the capillary beds of the alveoli before they acquire a lumen. At the proximal end of the ligated pulmonary artery the collateral vessels actually penetrate the thick musculo-elastic wall to establish anastomoses which do not normally exist in rats

(180). All of these observations suggest the effect of chemical influences.

Rate of Development

The immediate expansion of pre-existing arterial collaterals has been demonstrated angiographically by a number of observers, for example, Winblad *et al.* (192), John & Warren (90), Longland (108). That persistent sympathetic activity can produce some delay has been shown by Ferris & Harvey (50) and by Mulvihill & Harvey (125), among others. The existence of a later and slower phase of growth has been realized for a long time. For example, in Nothnagel's (129) experiments it took at least 6 days after interruption of the femoral artery below the profunda and circumflex in rabbits, before Teichmann's injection mass could be made to penetrate beyond the ligature. Mention has previously been made of the sudden increase in relative size of the collateral vessels, as compared with the bronchi as a reference, after the fifth day following ligature of the pulmonary artery in the rat (188).

Quantitative flow data are relatively sparse. The problem was approached in various collateral beds by Eckstein *et al.* (47) using as a measure not only the pressure beyond a point of occlusion, but also the retrograde flow at intervals varying from less than 1 hour to many months. In general, in the femoral and carotid distributions, the collaterals opened rapidly, for example, to near maximal levels within 1 hour, while the process took several hours to a week to attain a comparable relative increase in the coronary circulation. When both the femoral arteries and veins were ligated there was an increase in retrograde pressure and flow as previously observed by Holman & Edwards (78), and Eckstein *et al.* (47) found the same to be true in the coronary arteries upon ligature of the coronary sinus. The conservative effect on tissue of ligating the corresponding vein when a major artery is interrupted has been stressed by Makins (111) and confirmed by Reichert (143).

In the lung there is at least a 30-fold increase in arterial collateral circulation, whether or not the veins are also ligated, 16 months after interruption of the pulmonary artery (fig. 12), and there is evidence still of a continuing rise at this late time, although this is much less steep than in the first 2 months. Indeed a highly pertinent question is what brings the growth of these collateral vessels, or of any vessels, to an end.

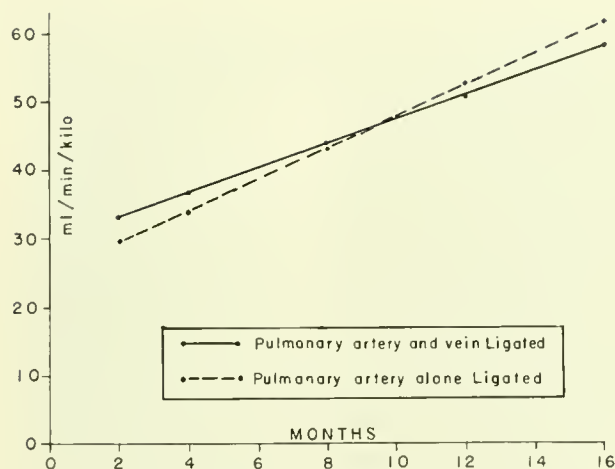


FIG. 12. The calculated regression lines for rates of increase of collateral blood flow are plotted when both pulmonary arteries and veins are ligated (solid line) and when the pulmonary artery alone is interrupted (broken line). These are remarkably congruent; this indicates that the collateral veins can expand at least as rapidly as the arteries. The data for "artery alone" have been recalculated in ml/kg/min from a paper by Bloomer *et al.* (20). An adjustment for nitrogen shift in the bronchspirometry has also been made and this has made possible the construction of the graph, using also data previously published by Vidone & Liebow (183).

In certain other situations progressive increase in expansion of collateral beds can take place for at least 1 year and possibly longer. As discussed previously, this has been observed in the arterial collateral circulation related to an arteriovenous fistula.

Regression of Collaterals

That preformed collaterals can open rapidly and disappear as quickly when the stimulus to their formation is abrogated has been shown angiographically by Winblad *et al.* (192) and John & Warren (90).

As a collateral bed develops, certain of its components tend to enlarge and to persist as major channels, while others regress. This was noted in successive angiograms after ligating the femoral artery in the rabbit (108). North & Sanders (127) found in the ear of the mouse that when continuity of an interrupted vascular channel was regained certain minor collaterals regressed.

Even collaterals of long standing remain only so long as the stimuli that led to their expansion are maintained. Boshier *et al.* (22) observed regression of collateral circulation associated with a peripheral arteriovenous fistula by comparing angiograms im-

mediately and again 6 weeks after fistulectomy; some regression was apparent as early as the fourth or fifth day. Anatomically the collaterals in regression were described as showing marked subendothelial proliferation. The results after fistulectomy were similar to those after ligation of the major participating vessels in the fistula, and this was considered further evidence against the "tissue need" theory. Winblad *et al.* (192) Schoop (156) and Hasse & Schoop (70) noted the regression of collaterals after adequate thrombo-intimectomy or bypass grafting in major systemic arteries. Similar phenomena were described by Jacobson & McAllister (89).

Arterial Versus Venous Collaterals

"Nature has been more prodigal in the provision of alternative venous and lymphatic routes than she has been in arranging for arterial collaterals" [Learmonth (96)].

In the lung the stimuli to the development of arterial and of venous collaterals are independent. This is true not only where mechanical forces seem dominant as in the expansion of pre-existing collaterals, but also where chemical influences appear to be pre-eminent as in the case of newly formed transpleural vessels.

When both arteries and veins are compromised under appropriate conditions, both arterial and venous limbs of the collateral circulation will expand. This has already been discussed for the lung. In segments of small intestine transplanted to the subcutaneous tissue by the Florey-Harding method (128) both arterial and venous collaterals appeared when the original mesenteric vascular pedicle was severed.

It is of interest that in these experiments the venous collaterals seemed to develop to a larger size more quickly than the arterial. Similar observations had been reported by North & Sanders (127) in the ear of the mouse. The veins seemed to expand within 24 hours, while it took 4 to 5 days for visible expansion of arteries to take place. Quantitative data are available for the lung. When both the pulmonary arteries and veins are interrupted, the collateral blood flow is approximately the same as when arteries alone are ligated (fig. 12). This means that expansion of the venous collateral can at least keep pace with that of the arterial.

In these experiments arteries became joined to arteries, and veins to veins, but there are circum-

stances where arteriovenous connections develop in newly formed circulations, as in the rabbit ear chamber (36). It is of interest that such arteriovenous shunts are normally present in the rabbit's ear (34).

Some Effects of Collateral Circulation

Blood supply arriving of necessity by way of collateral routes is usually not so efficient as the original in maintaining full function. Rarely it may exceed the needs of the tissue, as in association with large peripheral arteriovenous fistulas, and in the lungs, as has been described. In the latter, however, it nevertheless falls short of normal pulmonary perfusion that is carried on in the service of the body as a whole.

Certain special effects of collateral circulation occur under pathological circumstances, but these can only be mentioned in passing. Thus, in the lung, the seat of severe fibrosing disease such as bronchiectasis, where large precapillary anastomoses are formed between bronchial and pulmonary arteries, the higher pressure in the former tends to shunt the pulmonary arterial blood into normal tissue where oxygenation can occur. Consequently, there may be no peripheral arterial desaturation. When sufficiently numerous, these connections may contribute to an increased resistance to the output of the right ventricle. Reverse flow in pulmonary arteries from the periphery via these anastomoses has also been demonstrated, by analysis of gases in blood drawn from catheters placed within such arteries, and by angiography (103), and most convincingly by aortography (3). In the last mentioned a radiopaque substance introduced above the origins of the bronchial vessels has been shown to fill the pulmonary arteries retrogradely.

The hepatic circulation bears certain analogies to the pulmonary. Enlargement of the hepatic arteries has been demonstrated in cirrhosis, and the suggestion has been made that they may contribute to portal hypertension as a consequence of more direct connections with the portal veins (68).

Bronchial veins so enlarged that their valves become incompetent have been demonstrated in pulmonary emphysema, and the possibility of reverse flow of blood, i.e., from the azygos system into the pulmonary veins has been inferred (100, 114). Such shunting has also been considered as an explanation of the cyanosis sometimes encountered in fibrosis of the liver (27). Enlargement of bronchial veins, probably as a result of high pressure in the azygos

system which may carry a large volume of blood bypassing the liver, has been demonstrated by injection.

Structure of Collateral Vessels

It is now well established that vessels reflect in their structure the mechanical conditions to which they are subjected. As early as 1883 von Recklinghausen (142) stated in his textbook that as collaterals carry more blood, they become thicker and more tortuous. That there is both hypertrophy and hyperplasia of smooth muscle in the larger collaterals was described and illustrated by Nothnagel (fig. 9). Fischer & Schmieden (51) provided an experimental demonstration of adaptive changes in larger vessels subjected to altered circumstances of pressure and flow. When a segment of external jugular vein was inserted into the course of the carotid artery of a dog, it became reduced in caliber, firmer, and as much as two or three times thicker. Histologically, the media was shown to contain much more muscle and connective tissue (fig. 13). The medial elastic fibers were thought to be reduced, but this was not convincingly demonstrated. The adventitia also was seen to contain denser connective tissue. The intima generally remained unchanged. The trunk of the pulmonary artery, when subjected to a sufficiently increased pressure, becomes markedly thickened with an increase both in elastic tissue and smooth muscle (105, 145).

With the enlargement of small arteries as they become able to carry more blood there often appear remarkable aggregates of longitudinal smooth muscle fibers that dissect or even replace the internal elastic lamina, and that may lead to the subtotal or even complete obliteration of the lumen. Such vessels have been most extensively studied in the lung and in many types of chronic pulmonary disease where bronchial collateral circulation is characteristically increased (109, 187). Some have called these "Sperrarterien" (72-74, 93) and have thought them to possess a regulatory function in relation to their anastomoses with pulmonary arteries. In more general terms it may be said that longitudinal muscle tends to increase in other small muscular arteries with an augmentation in the blood that they carry, as in the bases of the cardiac valves in rheumatic fever, in the vasa vasorum of the aorta in syphilis, and in the intercostal vessels as they traverse adhesions to enter the lung. Probably the hypertrophy and hyperplasia of muscle is in fact a response to increased

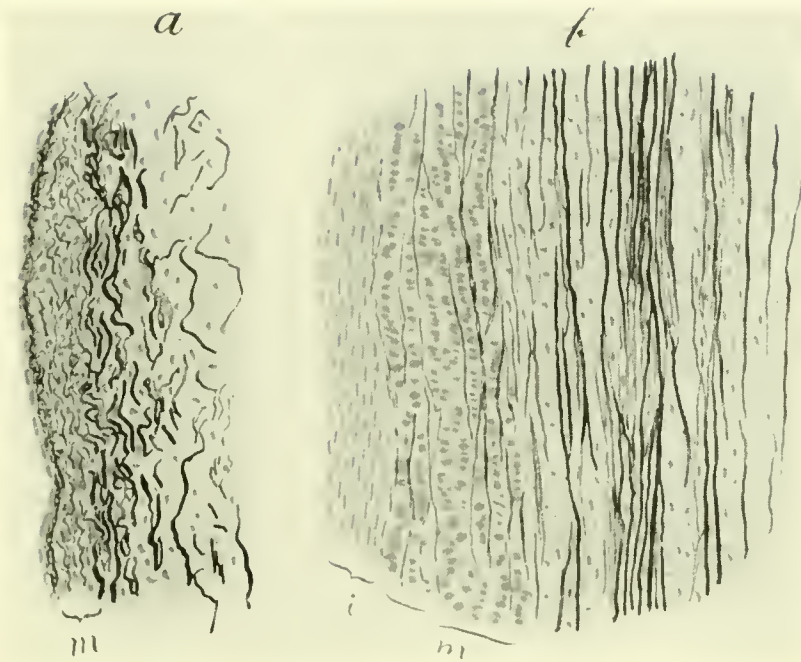


FIG. 13. Adaptive changes in a segment of jugular vein which had been inserted into the course of the carotid artery for 86 days. At left is shown the appearance of the vessel before its exposure to the higher pressure. Key: i—intima; m—media. [From Fischer and Schmieden (51).]

tension which, in general, appears to increase the tone of muscle (9, 16, 171). This has been suggested for the increased muscle characteristic of bullae in pulmonary emphysema, the walls of which are under stretch consequent to air trapping (106). A brilliant experimental demonstration of this mechanism in small vessels has been provided by Weibel (187). In his experiment, increased tension in mesenteric vessels was produced by stretching the mesentery slightly and attaching it to the diaphragm. The inner longitudinal muscle then did increase to a remarkable degree.

Gaps in the internal elastic lamina of the large arteries serving as collaterals have been noted by several observers (102, 108). Some newly formed collaterals may possess relatively little or no elastica (161).

Newly formed collateral vessels that develop from capillaries, as for example in the adhesions between visceral and parietal pleura, ultimately acquire a structure appropriate to their function as arteries or veins at the size which they ultimately attain (86).

The growth of muscle in the walls of vessels functioning as collaterals in the mesentery of the rat has been well described by Weyrauch & De Garis (189). They considered the stimulus to be increased blood volume. The tortuosity of the vessels was said to be the result of the fact that the muscle fibers do not grow in a single plane and this may be one factor to

account for the tortuosity of collaterals in general. They also described the appearance of muscle in vessels which they thought were newly formed.

Less well understood than the structural changes are the forces that bring them about. They are probably similar to those that govern the differentiation of arteries and veins from the retiform capillary anlagen of the early embryo, as previously discussed.

Measurement of Collateral Circulation

Attempts have been made to estimate the extent of collateral circulation by both anatomical and physiological methods. The former offers only a general and not necessarily reliable guide to the latter, in the sense that the size of a bridge cannot always provide a clue to the magnitude, nor even to the direction of traffic.

The early observers, such as Morgagni and Porta, made many excellent observations with the naked eye. Direct visual observation continues to be of value and details of the formation of smaller collateral vessels can be observed microscopically at intervals in the process of their formation, for example, in the ear of the living mouse (127). John Hunter (83) early used injection methods in his famous studies of the new blood supply to the stag's antler. Some of his casts of the vessels are preserved to this day in the Museum of the Royal College of Surgeons in London. Attempts have been made to quantitate

the results of the injections. This has been accomplished by some who have standardized an injection mass that does not penetrate through vessels of less than a known diameter. Important information has been yielded by such radiopaque materials as Schlesinger's (154, 155). Colored masses in gelatin or similar materials have also been used to inject tissues that have subsequently been cleared, for example by the method of Spalteholz (164). Materials that harden to provide casts of the vessels and which resist subsequent corrosion of the tissues have been useful in many applications. In the study of such casts, or other injections, certain critical points can be established, and the magnitude of the collateral can be estimated by whether or not the material has penetrated into particular segments of the system (147). Casts can be measured or weighed. Glass or plastic beads of graded sizes have been used to establish the size of vascular communications (2, 3, 126, 131, 137, 138, 162). With these materials overpressure must be avoided and the possibility of contamination must also be considered. Angiography, microangiography (11), and more recently cineangiography have become increasingly important with improvements of technique, especially since they offer a way of investigating the collateral circulation in intact animals. Quantitation can be achieved by such procedures as that of Longland (108), who counted the number of vessels in his angiograms that exceeded a stated size at a selected level. In the lung, a degree of refinement can be obtained by relating the vessels to the diameters of the bronchi which they accompany (188). The same can be done in any organ with an appropriate reference structure.

To measure collateral blood flow, direct and more or less indirect methods have been applied. The simplest perhaps is the collection of blood from the veins draining the part. This procedure is useful only if the tissue is supplied exclusively from a collateral source during the period of measurement, and if the veins carry away all or a known proportion of blood. These conditions cannot often be met. In man, plethysmography has been employed in the study of collateral circulation (193).

The collection of "backflow" from a vessel beyond a point of occlusion has been used on the presumption that it will increase if the vessels circumventing an occlusion come to carry an increased volume of blood. This principle has been extensively applied in the study of the coronary circulation (63). Upon opening the vessel beyond the obstruction the periph-

eral resistance confronting the blood in the collateral vessels is, of course, reduced, and the backflow can in no sense be considered an absolute measure of collateral blood supply. As a relative measure the principle is valid if no uncontrollable change, such as spasm, has occurred in the diameter of the vessel beyond the point of occlusion. Backflow then would reflect the pressure in the vascular bed in the distal arterial segment, which also is related to the extent of the collateral connections. Pressures as well as flows have been measured for this purpose.

Other "direct" measurements have been made by introducing such devices as the bubble flowmeter into the major feeders of the collateral bed (26). In such structures as the lung, attempts have been made to perfuse separately the greater and lesser circulations (151). Both procedures require extensive surgery, with denervation and possibly other disturbing factors.

In the lungs bronchospirometry and blood gas analyses, with temporary balloon blockade of a pulmonary artery and application of "mixing formulas" where indicated, can provide data on "effective" collateral arterial flow, i.e., blood arriving by systemic arteries that becomes oxygenated in the lungs (20, 52).

The fact that the temperature of a tissue bears a relationship to the quantity of arterial blood perfusing it in a unit of time has been used to measure collateral circulation (50). One source of error lies in the fact that blood flow is not necessarily distributed in a uniform manner through all tissues of a part, nor through all portions of a tissue.

The distribution of such dyes as Evans blue or Fox green or of radioactive materials, or "labeled" erythrocytes (138) in various vascular compartments has been used for qualitative detection of shunts, but under specific conditions. Isotonic solutions differing in temperature or conductivity from blood can be employed instead of dyes, and records similar to dye concentration curves can be obtained with appropriate sensing, amplifying, and recording devices.

Under special circumstances such methods can also be applied in a quantitative fashion. In the lung where an extensive bronchial collateral circulation represents a left-to-left shunt, originating as it does in the left ventricle and aorta, and returning from the lungs via the pulmonary veins to the left heart, introduction of an indicator material such as T-1824, Fox green, or radioactive iodinated serum albumin into the circulation produces characteristic altera-

tions from the usual in the arterial dye curve: A more rapid reversal of the downward limb of the first wave and a double-humped camel rather than dromedary recirculation curve. A known quantity of the indicator can be injected rapidly into a systemic vein, and concentration curves can be obtained simultaneously from the pulmonary artery and aorta by appropriate methods such as cuvette densitometry. The "left cardiac output" measured from the latter should exceed the "right cardiac output" calculated from the former by the volume of the collateral blood supply to the lung. This principle has been applied by a number of workers (38, 55, 56), but very rapid left-to-left recirculation introduces problems that may make this procedure inapplicable for quantitative use.

To measure collateral blood flow from extra-coronary sources to the heart by means of vessels in anastomosis with the coronary arteries, the dye has been introduced into the aorta above the orifices of the presumed collaterals and well below the origins of the coronary arteries in the sinuses of Valsalva. If collaterals exist, dyed blood will reach the coronary sinus by the collateral route before recirculation can take place. Quantitation has been attempted by comparing the peak concentrations in the aortic blood with that of the coronary sinus peak, or better, the areas beneath appropriate segments of the two curves (182).

Some Outstanding Problems

The problems of collateral circulation are inseparable from those of angiogenesis, "histodynamics" in Thoma's sense and hemodynamics in general. Methods for study have advanced notably, but new developments can be expected to accelerate progress. Catheters, as used currently for measuring pressures and in obtaining dye concentration curves, carry inherent artifacts. Accurate sensing units sufficiently small so as not to interfere significantly with blood flow are needed for both purposes.

It is clear that many of the basic mechanisms must be essentially physicochemical. These must underlie the molding influence of mechanical forces on the structures of vessels. They must also be responsible for what is now vaguely recognized as "tropism." None of the essential chemical information is yet available to explain how, in a newly formed collateral bed, arteries are joined directly to arteries and veins to veins, with no arteriovenous connections, while the latter are constantly present normally in certain other parts.

John Hunter's (185) remark of 1785 still well defines the present state of knowledge: "All the uses arising from the anastomosing of the vessels are, perhaps, not yet perfectly understood; general reasons can, I think, be assigned for them, but these will not apply to all cases; it is something, therefore, more than we are yet acquainted with."

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Methods of measuring blood flow

KURT KRAMER

Physiologisches Institut der Universität, Göttingen, Germany

WILHELM LOCHNER

Physiologisches Institut der Medizinischen Akademie, Düsseldorf, Germany

E. WETTERER

Physiologisches Institut der Universität München, München, Germany

CHAPTER CONTENTS

Varied Methods and Instruments for Flow Measurement
 Admixing Methods for Measurement of Regional Blood Flow
 Flowmeters: Their Theory, Construction, and Operation

Perhaps no other field of physiological methodology encompasses such a variety of physical and chemical principles as that of flow measurement. Principles of measurement may be and have been developed from almost every topic in physics textbooks: mechanics (solid, liquid, and gas), sound, electricity, magnetism, optics, thermodynamics, and atomic physics. For this reason we have divided the duties of this section and each author has taken the field of his choice; or, more correctly, two authors have chosen and one (K. K.), like Cinderella, has made do with the remainder.

We have set ourselves the task first to review these various principles, or at least to sketch their historical development,

and second to acquaint the reader with the manner in which each method fits the special purposes of the investigator.

We have attempted to give a more detailed description of modern techniques or older ones which are still in use today; in this we have tried to present not so much an account of technical details of a piece of apparatus as special suggestions which will facilitate its use, permit judgment of its reliability, and guard against sources of error. What we take for reality sometimes changes so that it is often difficult to distinguish that which is true only for the moment from that which will endure.

If older methods no longer in use today are mentioned, it is to point out particular disadvantages which caused them to be abandoned. In this way we hope to guide the young traveler who might otherwise take these fruitless paths again.

K. KRAMER

W. LOCHNER

E. WETTERER

I. Varied methods and instruments for flow measurement

KURT KRAMER

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OUTFLOW MEASUREMENTS

Venous Outflow Collection

THE SIMPLEST and most reliable way to measure mean blood flow of an organ consists in the collection of blood from an opened vein into a graduated cylinder over a measured period of time. Several venous outflow recorders with intermittent indication of flow rate have been designed (44). In Gaddum's model (34) blood from the opened vein runs into a cylinder, the bottom of which is automatically opened after known periods of time. The collected volume in the cylinder may be recorded making use of Brodie bellows, strain gauges, or other devices for measuring volume or pressure. The Gaddum principle is in fact a continuous recording of graduated cylinder and stop watch readings. The dimensions of the apparatus do not allow measurements lower than 10 ml per min. Readings every 2 sec furnish reliable results. The diameter of the cylinder must be adapted to the amount of blood expected to leave the vein per unit time. The reliability depends mainly on the rapidity of emptying the cylinder between collection periods.

Drop Recording

Measurements of flow rates lower than 2 ml per min can be obtained by recording every drop of blood leaving the blood vessel. In most devices the drop closes an electric circuit thereby giving an electromagnetic signal. Enumeration of drop signals, however, is inaccurate and troublesome. Therefore construction of an instrument that records time elapsing between two drops was a great improvement in the method. In 1935 Fleisch (29) described an apparatus in which a motor-driven lever is moved up on a smoked drum until the drop falls. Closure of the electric circuit by the drop initiates the interruption of a coupling link between motor and lever so that the lever returns to its original level. The next period of measurement always begins after 0.12 sec regardless of the height of the lever. It is obvious that such a recorder is more complex than the simple marking apparatus and its construction involves a high degree of precision work.

With the development of electronics a principle was applied in which the time measurement was performed by measuring the increase of voltage on a condenser during the time between drops. The drop initiates a sudden breakdown of the condenser charge.

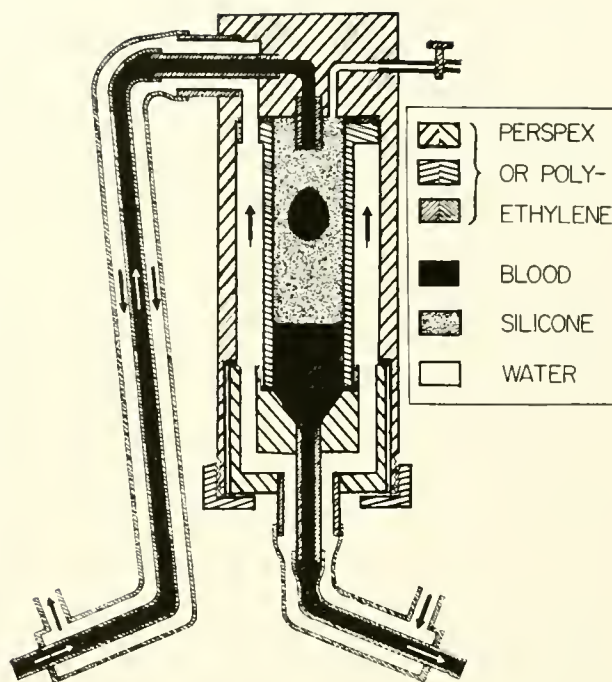


FIG. 1. Schematic drawing of the drop chamber according to Lindgren. A concentric water jacket maintains constant temperature of the blood. [From Lindgren (62).]

The voltmeter records deflections which are proportional to the time between two drops (63a).

Drop recording has been used mainly to measure venous outflow. The drawback of all outflow measurements is loss of blood and the necessity for prompt reinfusion. A definite improvement therefore was the introduction of a drop chamber that can be used in a closed circulatory system (58). The blood from a vein entering the drop chamber falls in drops between electrodes to the bottom and returns to the distal part of the dissected vessel. The air cushion does not seem to introduce any disadvantage in the return of blood to the vein.

Since electrolysis at the electrode contacts and their coating with coagulated blood often makes readings unreliable, a photoelectric drop recording device has been constructed. A combination of both improvements—the enclosed drop chamber and the photoelectric recording of drops—seems to be the best of the fairly simple methods (fig. 1). Lingren's device (62) uses a drop chamber filled with silicone instead of air, thereby avoiding elastic effects especially important in arterial blood flow measurements. In recording of pulsatile arterial flow, one should consider also that the device may impair the transmission of pulse waves to the peripheral arterial bed, thereby diminishing original mean flow rate.

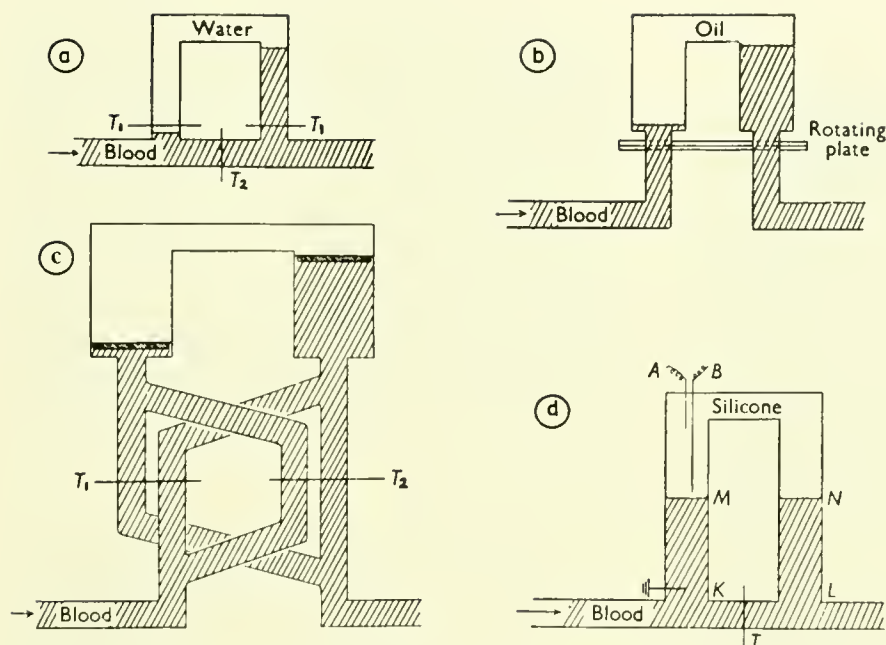


FIG. 2. Schematic drawings of direct recording flowmeters derived from Volkmann's and Ludwig's principles. [From Dawes *et al.* (22).] *a*: Volkmann (1850). Open T_1 , close T_2 , and time movement of blood through U-tube. *b*: Ludwig (Dogiel, 1867). Time movement of blood through one chamber and then reverse chambers by hand. *c*: Pavlov (1887). Time movement of blood through one chamber and reverse direction of flow automatically by opening electromagnetic tap T_1 and closing T_2 . *d*: Dawes *et al.* (22) Close T and time movement of blood between electrodes A and B ; restore blood levels by opening T .

METHODS BASED ON LUDWIG'S PRINCIPLE

Volkmann, (81) in 1850, was the first to measure blood flow per unit time in arteries (fig. 2*a*). His device consisted of a U-tube inserted in an artery. The U-tube could be bypassed by two 3-way stopcocks. When measurements were taken, the U-tube was filled with saline. After turning both stopcocks simultaneously the blood flowed through the U-tube, the time was measured between the moments when the blood entered and left the U-tube.

This method obviously did not allow continuous measurement of blood flow. Another drawback was the repeated infusions of saline with each measurement of flow. Therefore Ludwig and colleagues (see 24) modified Volkmann's device (fig. 2*b*). In their version, the upstream limb of the U-tube was filled with oil and the downstream one with blood. The tube itself could be turned by hand through 180° , to connect the two limbs alternately to the distal and proximal ends of the artery. The blood was allowed to enter the upstream limb and the tube had to be turned when the oil content reached the entrance to the distal arterial connection. Each turn was marked on a smoked drum, thereby recording blood flow continuously. Apparatus based on Ludwig's principle have been constructed with many modifications and are still in use (6, 12, 6g). The directness of the measurement of flow can be regarded as the main reason for its popularity. In Ludwig's laboratory Pavlov

(70) developed in 1887, a self-recording flowmeter based on the same principle. To avoid manipulations for reversing the direction of flow, he designed his meter so that blood could be made to enter alternately either limb of the U-tube by opening and closing electromagnetic taps. (see fig. 2*c*). The taps were automatically operated by means of floats in both limbs moving with the direction of flow and closing contacts in the electromagnetic circuit when the rising float reached the top of its limb.

The Pavlov type flowmeter has been used in numerous modifications. The U-tube can be made very small for low flow rates. To avoid electrical contacts within the blood stream the electromagnetic taps can be controlled by photoelectric relays (63).

An ingenious device based on Ludwig's principle has recently been described by Dawes *et al.* (22) (fig. 2*d*). The upper part of the U-tube is filled with silicone oil, the lower part of both limbs with blood. The bypass can be closed by an electromagnetic tap. In the inflow limb of the U-tube, two electrodes which operate a relay for opening and closing the electromagnetic tap of the bypass are inserted with a distance between them, such that about 1.5 ml of fluid is enough to cover both contacts. When blood enters the proximal limb it touches one electrode. After 1.5 ml more have entered, the other electrode is connected with the first, thereby closing an electric circuit and setting a relay causing the tap to open. This allows the blood which entered the proximal limb

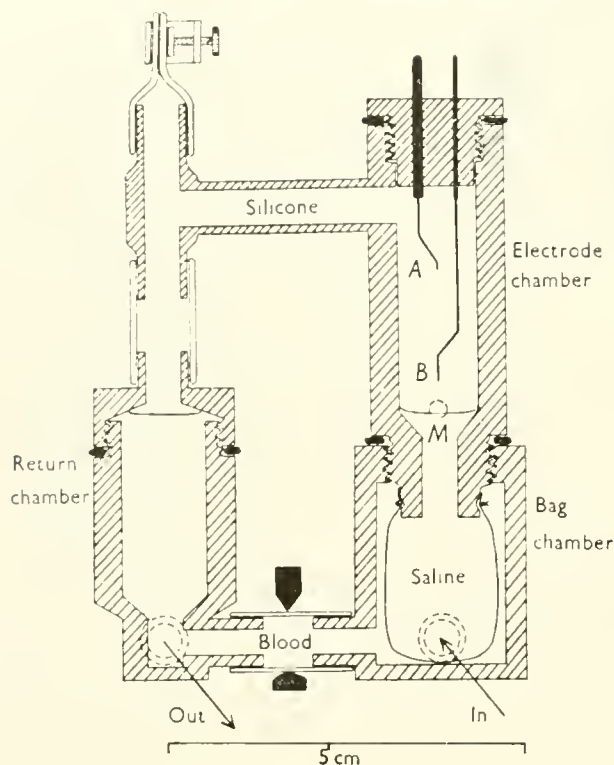


FIG. 3. Sectional view of the Dawes' flowmeter. The chambers are made of Perspex, the washers of Portex sheet, the connecting tubes of rubber, and the electrodes of silver wire. The bag is molded of rubber solution on a form (see text). [From Dawes *et al.* (22).]

to return to the arterial stream driven by a pressure difference between the two limbs. This pressure difference is supplied by the density difference between blood and silicone oil. Therefore the authors have called their apparatus "density flowmeter." The technical details are more involved than the description of the principle indicates. As can be seen from figure 3, in the actual device blood is not allowed to enter the electrode chamber. A rubber bag filled with saline placed in the lower part of the proximal limb is compressed by the inflowing blood, emptying its contents into the part of the limb containing the electrode.

The apparatus of the dimensions given in figure 3 can measure blood flow at rates as high as 45 ml per min with an absolute accuracy of ± 4 per cent. The pressure drop does not exceed 3 to 4 mm Hg at maximum rates. The dead space to be filled with blood amounts to about 4 to 5 ml. The range of flow may be extended by using larger measuring chambers.

For measurement of time intervals any kind of ordinate writer (29) can be used. Gaddum's drop-timer (1938) was used by the authors (44).

A still simpler self-recording flowmeter making use of a single electromagnetic tap in the bypass was first described by Dawes *et al.* and has been constructed recently by Wretling (88). When the bypass is closed the blood enters the U-tube, consequently bulging a membrane in proportion to the volume flow. The displacement of the membrane is recorded by a lever on a smoked drum. The tap is automatically opened every 2 sec so that blood in the U-tube returns to the artery, allowing the membrane to return to its original position. Then the cycle begins again with the closing of the tap. Since the lever indicates blood flow per 2 sec, the record gives direct readings of flow rate.

BUBBLE FLOWMETER

The bubble flowmeter developed by Soskin *et al.* (75) consists of a glass tube of known caliber and

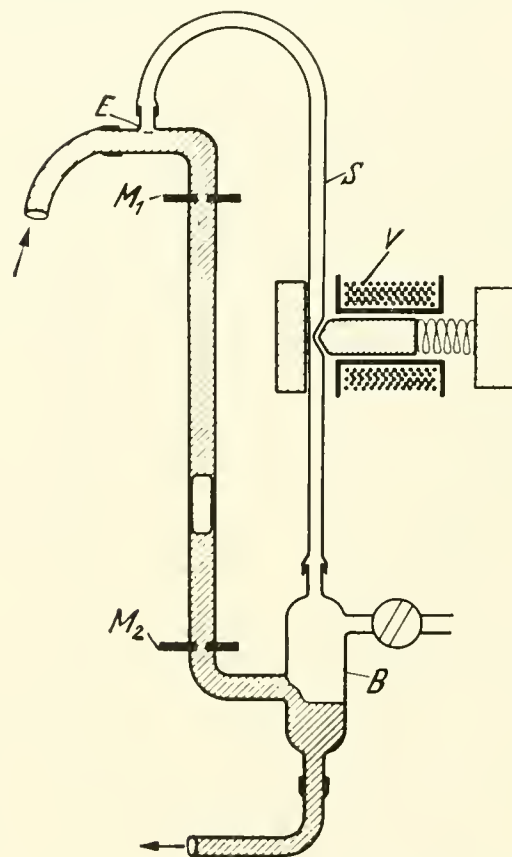


FIG. 4. Schematic drawing of a bubble flowmeter: *B*, bubble reservoir; *E*, entrance of the bubble into the flowmeter; *M*₁*M*₂, measuring points (platinum electrodes) for timing the passage of the bubble; *S*, rubber tubing; *V*, magnetic tap used as automatic bubble injector. [From Röckemann (72).]

length which is inserted into the blood stream from an artery. Near the proximal end of the tube an air bubble of such a size as to completely fill a short section of the tube is injected and time required for the bubble to pass the length of the tube is recorded. Near the distal end of the tube the bubble is caught in a trap. The rate of flow is calculated from the ratio of volume and time, as is done for all the foregoing recorders.

To utilize this principle for continuous recording of blood flow, an automatic injector for air bubbles, automatic removal of the bubbles after they pass the tube, and a recorder of time required for passage of each bubble are necessary. Several solutions of the problem have been proposed (13, 15, 33, 57, 64, 65, 87).

A recorder for the passage time of the bubble which uses photoelectric signals caused by the bubble when passing a light source and phototube was introduced by Selkurt (73). Baumgartner *et al.* (11) added an automatic bubble injector, the operation of which is timed by the passage of the bubble past the photocell detector. A schematic drawing of a recent model (72) is seen in figure 4. They also studied the over-all properties of the principle. They could not confirm the assumption that blood and bubble velocity are equal. Rather, they found that at low flows the bubble velocity is less and at more rapid flows it is greater than the blood velocity. The reasons for these deviations are complex. At high flows the bubble seems to lose contact with the wall and to move in the faster axial stream of the blood. Viscosity influences the bubble velocity somewhat but not seriously. Maximal deviations are not greater than ± 5 per cent. However, if an accuracy within 1 to 2 per cent is desired, they suggest calibration of the apparatus with blood of the animal. Pulsation is without influence on the calibration curve. They used a tube 3.5 mm in diameter and 35 cm in length. The resistance to flow in such a tube is low in comparison to that of the peripheral vascular beds. The maximal flow they studied amounted to 300 ml per min. At this rate the pressure gradient was not more than 4 cm of H_2O . This value is comparable with other methods used on opened vessels. The diameter of 3.5 mm cannot be much increased because at diameters of more than 4.5 mm the air bubble will not fill the flowmeter tube. Lengthening the tube increases the sensitivity of the measurement, but also increases resistance to flow. This fact is to be considered mainly in measurements of venous flow.

VENOUS-OCCLUSION METHODS

The principle of the venous-occlusion method consists in temporarily blocking the venous outflow from an organ which is enclosed in a plethysmograph. The blood that enters the organ via the artery is thereby retained and indicated as a volume increase by the plethysmograph.

In this way the method is an almost direct volume measurement per unit time and thus comparable in principle to those described in the foregoing paragraphs. Brodie & Russell (14), who first described the venous-occlusion principle, were aware of the main conditions to be fulfilled: "... It is obviously essential that the blockage of the vein must not be maintained so long as to impede the flow through the capillaries. Under all ordinary conditions the veins are never completely filled, so that it is possible to store up in them a small extra quantity of blood without checking the inflow into them from the capillaries." As long as the volume recorder indicates a uniform increase, the inflow is not impeded. Brodie's method was adapted by Hewlett & von Zwaluwenburg (56) to measure blood flow in extremities in man. A plethysmograph similar in construction to that of Mosso was used: a glass cylinder wide enough to enclose the hand and forearm, from which a rubber tube of small dimensions leads to the recorder. The whole system is filled with water to avoid volume errors due to temperature changes. The veins are blocked by applying pressure of 50 mm Hg into a pneumatic cuff placed on the upper arm.

Several modifications (79) of the original device have been described (8-10, 46). H. Barcroft's assembly is now most commonly in use (fig. 5). Mosso's glass cylinder is replaced by a conic metal tube. The hand is covered with a large surgical rubber glove which is fixed outside the plethysmograph to avoid leakage of water. Since any movement of the forearm will change the volume of water inside the plethysmograph, the circumference of the glove is stiffened by a diaphragm $\frac{1}{4}$ -inch thick. The diaphragm is bolted to a 2-inch-wide flange on the end of the plethysmograph by means of metal plates and wing nuts. (For further details see the original paper.) The pneumatic cuff is connected through a three-way tap with a reservoir of compressed air at 60 to 70 mm Hg. The three-way tap allows inflation of the cuff from the reservoir and deflation when it is opened to room air. Two or even four measurements can be taken in 1 min, if blood flow is high. At this rate of measurement the cuff is inflated for only 5 sec. It is found that

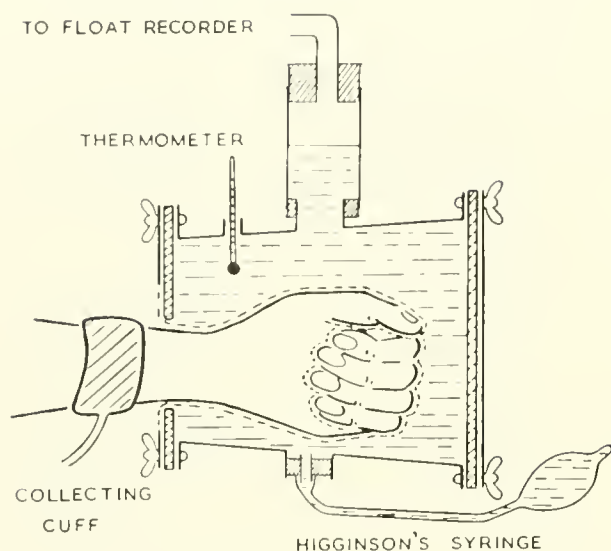


FIG. 5. Plethysmograph for the hand according to H. Barcroft. The hand is enclosed in a loose-fitting surgical rubber glove. [From Barcroft & Swan (10).]

during this time the volume of the hand increases uniformly, indicating that the venous reservoir is not filled to an extent which would impair capillary flow.

The recording system used in Barcroft's experiments consists of a small spirometer writing on a smoked drum. The rubber tubing connection between the plethysmograph and spirometer is filled with air. The use of a spirometer makes it necessary to have air in the rubber tubing connections between spirometer and plethysmograph. A small cylinder on top of the plethysmograph allows control of the water level of the apparatus. An electrically recorded tracing of spirometer movements is used in our laboratory making use of the electromagnetic principles applied in the rotameter recording technique (see below).

The use of small rubber cuffs as plethysmographs has been recommended recently by Dohm. Models suitable for measurements on forearm and calf, with which it is possible to secure good venous-occlusion records and to measure blood flow during muscular exercise, are especially useful on moving subjects (41). The plethysmographic cuffs are made of thin-walled rubber 5 cm wide. The filling pressure can best be about +40 mm H₂O and increase with 1 per cent volume changes of the extremity segment up to about 50 mm H₂O. The pressure was measured by a condenser manometer.

Avoiding any plethysmographic devices, Whitney (86) proposes the use of a strain gauge mounted directly on the limb. It records the changes of tension

due to changes in blood volume. This occlusion technique furnishes results not remarkably different from those obtained by using water or air plethysmography. Assuming that the limb is distended only in the diametrical direction, changes of circumference can be converted directly into volume changes. However, corrections for compression of the limb by increases in blood volume are deemed to be necessary.

A serious objection to the venous-occlusion method is discussed by Gaskell & Burton (35), who observed a decrease of blood flow in the dependent leg. These authors believe in a venovasomotor reflex elicited by distension of veins. Since the venous-occlusion method relies on the fact that blood entering the region of measurement is collected in the veins, thereby distending them, it is important to the validity of the method to study the influence of venous distension upon vascular reflexes.

Greenfield & Patterson (45) showed in experiments on the forearm at different states of venous distention that the blood flow, as measured with their venous-

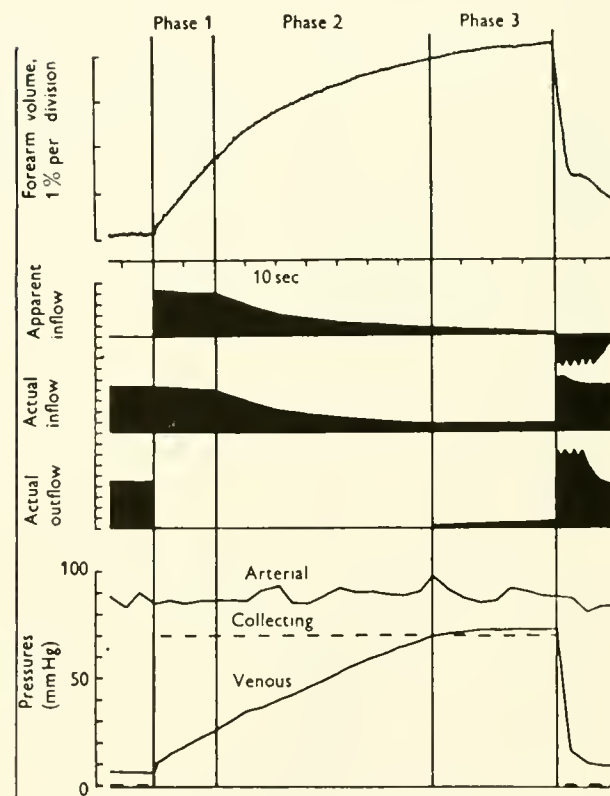


FIG. 6. Events during venous occlusion plethysmography. Actual inflow = actual outflow + apparent inflow. Each division on vertical scale for inflow and outflow represents 1 ml/100 ml of forearm per min. Total duration of collection: 130 sec. [From Greenfield & Patterson (45).]

occlusion technique, did not change. Even in states of venous congestion leading to 2 per cent increase of the limb volume, the blood flow was almost unaltered. Less than 1 per cent increase of limb volume is usually necessary in the application of the venous-occlusion method. Considering all this, they offer several explanations of Gaskell and Burton's findings.

Greenfield and Patterson give an instructive diagram of events during venous occlusion (fig. 6). In the first phase of occlusion the plethysmographic record shows a straight line increase indicating a constant inflow of blood into the extremity. In the second phase, the volume increase of the extremity declines asymptotically, indicating that the inflow of blood progressively decreases. This can be explained by the decreasing arteriovenous pressure difference. In a third phase the venous pressure reaches the occlusion pressure. A new equilibrium obtains in which there probably is a much lower blood flow through the extremity. The volume increase in the occluded region levels off.

The "afterdrop" (a decrease in venous pressure and limb volume which occurs on release of cuff pressure if the veins are distended) can be considered as a vasomotor phenomenon. It can also be explained on mechanical grounds. The release of the pneumatic cuff opens up an area of compressed veins thereby acting like a muscle pump on the underlying veins (2). [See also (1) and (82).]

Pulse Plethysmography

According to Fick's suggestion it is generally accepted that the first differential quotient of volume change in an extremity occurring during the course of the arterial pulse equals the change in the rate of arterial inflow, if the outflow is constant. Von Kries (60) and later Frank (31) used tachographs and plethysmographs on the forearm and measured changes of volume and of the rate of arterial inflow during the arterial pulse. A combination of pulse plethysmography and venous-occlusion technique was used by Burton (19, 27), Burch (16, 18), and others in order to obtain absolute values for flow rates during the time course of the arterial pulse in fingers and hands. The plethysmographic devices (cylinders, cuffs, recording systems) are adapted to the size of the extremities in question. The recording systems consist of capsules covered with thin membranes, the bulging of which corresponds to volume displacements and are recorded optically. [For details see (17, 66).]

Photoelectric Plethysmography

Measurements of transparency and reflectance of infrared light in skin areas furnish almost the same values for blood volume changes as do the direct mechanical methods (52-55). The calibration of such instruments involving calorimetric or venous-occlusion techniques cannot claim great accuracy. However, the simplicity of the experimental procedure allows the use of instruments adapted to special purposes not only in various skin areas but also on the surfaces of organs such as the brain or kidney. The latter, especially with its high blood content (about 23%), has been the object of blood flow studies utilizing the light absorption properties of Hb in the red and infrared regions. Procedures have been elaborated (59) that allow measurement of blood content in cortical and medullary areas of the kidneys, as well as total blood flow using dye dilution and oxymetric principles.

THERMAL METHODS

Thermostromuhr

Thermal methods of measuring blood flow are based on the principles of measurement of heat conduction. It is assumed that any condition leading to loss or gain of heat in the blood stream would depend among other variables on its volume flow. Gesell & Bronk (37) cannulated the blood vessel and let the blood pass through a tube surrounded by a concentric water jacket which was flushed by a constant flow of water at room temperature. The loss of heat from the blood measured by the temperature increase in the outflowing water was found to be inversely proportional to the volume flow of blood. Corrections were of course made for different blood temperatures. The response to changes in flow is slow—of the order of 1 min.

A few years later H. Rein (71) constructed his thermostromuhr, which was made for use on unopened blood vessels. This method was regarded as a great improvement both as to lag time and convenience.

The original conception of the thermostromuhr was based on the assumption that an alternating current of high frequency applied to a blood vessel would heat the blood radially. The temperature rise (ΔT) of this disc of blood would then be proportional to the product of square of the current (I^2) and electrical

resistance (R) and inversely proportional to the blood flow (I) and specific heat (c). Measurements of blood flow using a device with two thermojunctions placed on each side of a pair of heating electrodes seemed to justify the above assumptions, and permit using the following equation:

$$V \cdot c = \frac{I^2 \cdot R}{\Delta T} \cdot 0.239 \quad (1)$$

According to this equation, the calibration curve is hyperbolic. This type of curve has actually been found in all thermostromuhr devices. However, quantitative measurements of ΔT (3) show values about ten times higher than expected. This finding indicates that the assumption of a uniformly heated cross section of the blood vessel is not valid. The error in determining ΔT is found to result from heating the vessel wall much more than the blood. Due to the complicated arrangement of electrical resistances to high-frequency current in the wall, the liberation of heat in the blood column amounts to only 10 per cent in arteries and 20 to 40 per cent in veins (83). The original assumption, therefore, must be revised: the radial heat gradient is directed from outside to inside the vessel and not, as suggested by Rein, from inside to outside. The basic principle by which the stromuhr measures flow is the change in T in the vessel wall with blood flow, because of cooling it by the blood stream. Findings based on this assumption are in good agreement with the earlier results obtained with the direct current method, showing that there is no basic difference between the methods (4, 5, 74, 77).

Further studies (3) on heat dissipation in the wall of the vessel and in the blood stream have revealed a temperature profile of complex nature.

The temperature gradients are directed from outside to inside the vessel radially and also along the length of the wall both upstream and downstream with highest temperature underneath the heating electrodes.

This temperature profile, however, is not symmetrical for two reasons: first, since heating electrodes are attached to a segment of the wall, the temperatures measured in the plane of the heating electrodes are higher than in a plane at an angle to it; second, since the blood stream cools the upstream wall section more than the downstream section, the temperature profile is lengthened in the downstream direction.

The temperature profile changes with blood flow. The asymmetry of temperature distribution along the wall of the vessel increases with decreasing blood flow. The temperature of the upstream section changes

less than that of the downstream section. It is this fact which makes the device a flowmeter.

From Gregg's investigations (43, 74) on direct current stromuhrs it was expected that pulsations of the blood stream should distort the temperature profile in an unpredictable manner. Wever & Aschoff (84), working with a stream having large pulsations, found that thermojunctions arranged at an angle of 90° to the heating electrodes yield false readings which are opposite to those obtained at an angle of 0° . The practical application of these studies has led to the construction of a device using ring electrodes, by which temperatures of the complex profile are averaged, and errors due to pulsation are avoided. These electrodes also compensate for errors resulting from nonlinearity of the calibration curve (fig. 7). Since the highest temperature exists on the outside of the vessel wall, any uncontrolled heat dissipation to the outside of the unit would lead to an undetectable error of measurement. In the new models (3), a double wall including air for thermoinsulation is introduced.

Where backflow occurs, the deviation in the measurements is always in the direction of increasing flow. The effect of backflow can be diminished by means of asymmetrical placement of the thermojunctions (77). When the downstream thermojunction is placed close to the heating electrodes and the upstream junction is farther off, the backflowing blood heated during its passage through the hot vessel wall will reach the upper junction later and will have less influence on the measurement.

Although methods based on the thermostromuhr principle have been abandoned during the last decades because of inherent inaccuracies (7, 25, 26, 43), the new analysis given by Aschoff and Wever has revived interest in the matter.

Skin Blood Flow Measurement Based on Thermal Conductance Measurement (20, 32, 48-51, 85)

Since the heat produced in animals and humans is transported mainly by blood flow, the heat flow of a defined area of the skin is related to blood flow through it. However, it is obvious that any change of temperature gradient, such as that induced by changes of the surrounding temperature, will influence the heat flow and therefore invalidate the measurement of blood flow. The best values are obtained with devices which measure heat flow and temperature gradient simultaneously.

The following equation gives a measure of blood

flow from the relationship of these two variables in the form of a thermal conductance coefficient:

$$k = \frac{\dot{Q}}{T_c - T_{sk}} \quad (2)$$

where \dot{Q} equals heat flow in (cal cm² sec), T_c = core temperature and T_{sk} = skin temperature in °C. The dimension of k is calories per square centimeter second °C. The T_c as measured does not always represent the temperature of the arterial blood in the region under study. Heat may be lost during the passage of blood from the core to the site of measurement. Hensel (50) points out that, among other things, the special geometry of the skin area, insulation, local metabolism, and countercurrent heat exchange between arteries and veins may modify k without changes of blood flow.

If it is possible to keep these variables constant, relative changes in blood flow in skin areas can be estimated by measuring k . Several methods are proposed. The measuring device should avoid the "reaction-error" which would occur if calorimeter devices are used with large heat capacities and temperatures different from those of the skin (48). However, it is necessary that the heat resistance of the device be made much lower than that of the skin, the resistance of which is determined by the blood flow.

A device (85) that fulfills the above conditions consists of a cork plate 1 mm thick covered with two silver plates with two thermojunctions. The unit is fixed tightly on the skin. The temperature gradient measured between these plates is proportional to \dot{Q} , the heat flow from the skin. The temperature difference $T_c - T_{sk}$ is measured by connecting the skin thermojunction with a third junction placed in the mouth or rectum. The quotient $\dot{Q}/(T_c - T_{sk})$ is measured by a bridge circuit or by a ratiometer. \dot{Q} can only be measured if the thermal conductivity of the cork plate is known. This value must be determined experimentally. Synchronous measurement of k and blood flow of the finger with the venous occlusion technique furnish a fairly good proportionality. This was found at different room temperatures (15–30 °C) as well as at different skin and rectal temperatures. Also, insulation of the arm did not influence the measurements. It seems therefore that, according to Aschoff and Wever's results, blood flow is the main factor determining k .

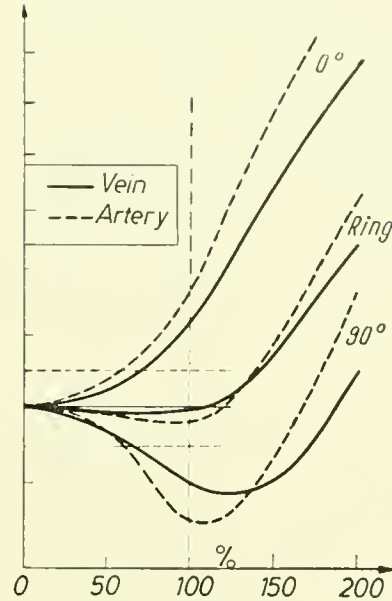


FIG. 7. Measurements with original Rein elements and Aschoff and Wever ring-element. Figure shows effect on flow readings when heating electrodes are placed at 90° and 0° to the thermojunctions. The compensating effect of a ring unit in which the thermojunctions are fixed on silver rings surrounding the vessel is shown to be effective for pulsations up to 120% of mean flow. *Abscissa* = oscillations in percentage of mean flow. *Ordinate* = thermostromuhr readings. [From Wever & Aschoff (84).]

Flowmeters Based on the Measurement of Thermal Conductivity

In 1921 the mathematician Carslaw showed that when a special source of heat is surrounded by an infinitely extended mass of material a steady state is approached in which the relation between heat production, such as that generated electrically, and heat loss is described by the equation:

$$I^2 R = 4 \pi r \Delta T \lambda \quad (3)$$

where I = electric current heating a filament with the resistance R , r = radius of the sphere, T = temperature of the sphere, and λ = the thermal conductivity constant.

In application to our problem we have to consider that λ , because of the complexity of the tissue, is not a simple constant but depends on several parameters of the tissue under study (80), and most importantly on blood flow. This dependence on flow provides the basic principle for measurement with this type of flowmeter. Experimental data (42) provided by measurements of ΔT on living organs have shown that a

linear relationship exists between blood flow and the apparent increment of λ . Direct readings of λ may be recorded (42) by keeping T constant through variation of I . It should, however, be borne in mind that only relative values for blood flow can be obtained. The principle can be applied either to surfaces or to inner regions of organs. For these various applications several types of instruments have been developed. As an example, for measurements of blood flow through deep layers, heat source and temperature measuring units are contained in a needle (38, 39, 42, 47, 68).

Hensel's modification shown in figure 8 contains both thermojunctions within the needle, one at the tip together with the heating wire, and the other at the middle of the needle. According to Graf & Rosell (40), reliable measurements are obtained only when the tip of the needle is placed in close proximity to a vessel, either an artery or vein. This condition is checked by comparison of λ -values obtained in the ischemic and normal state which should be in the order of 1×10^{-4} cal per sec cm C. Lower values

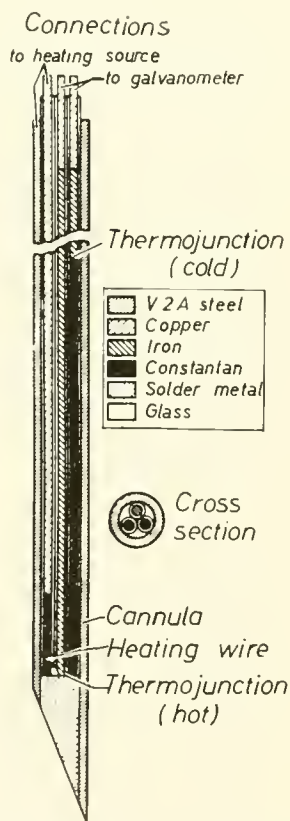


FIG. 8. Schematic drawing of longitudinal and cross sections of Hensel's needle for measuring thermal conductivity in tissue. [From Hensel *et al.* (47).]

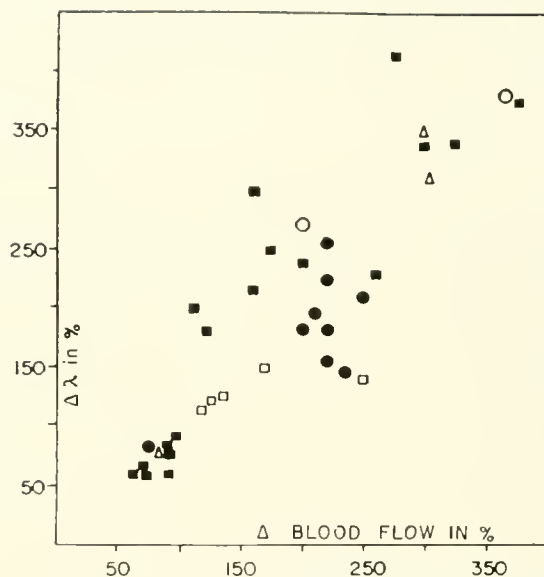


FIG. 9. Relation between thermal conductivity increments ($\Delta\lambda$) and blood flow in muscles of the cat's hind limb. Changes in blood flow were induced by intra-aortic infusions of adrenaline and acetylcholine and by hypothalamic stimulation. Four experiments marked with different signs. [From Graf & Rosell (40).]

indicate that the tip is placed too far from the vessel. This remote position would also result in a slow response to blood flow changes. A plotting of direct recorded values of blood flow through a hind limb of a cat and values obtained with Hensel's needle show that the percentage changes of λ accord well with the percentage changes of direct measurements. However, the above-mentioned condition of a conductivity increment of at least 1.0×10^{-4} cal per sec cm C was fulfilled (fig. 9). The advantage of the device lies in the fact that it can be used in humans without interfering with the normal state of blood flow.

To record blood flow on organ surfaces, as on skin, brain, or eye, several modifications of a "surface thermostromuhr" have been constructed. A. C. Burton has utilized the principle of electrical resistance changes with temperature. "Two flat resistance coils, the smaller a central disc and the larger a ring about it, with an insulating gap between, form the two arms of a Wheatstone bridge. These coils are of wire which has a high temperature coefficient of resistance, while the other two coils of the bridge are of constant resistance. The battery supplying the bridge is arranged to drive current through the two 'skin' coils in parallel. Since the central coil is of lower resistance, greater heat is generated since the current is greater in it, and as a result it will reach, in the thermal steady

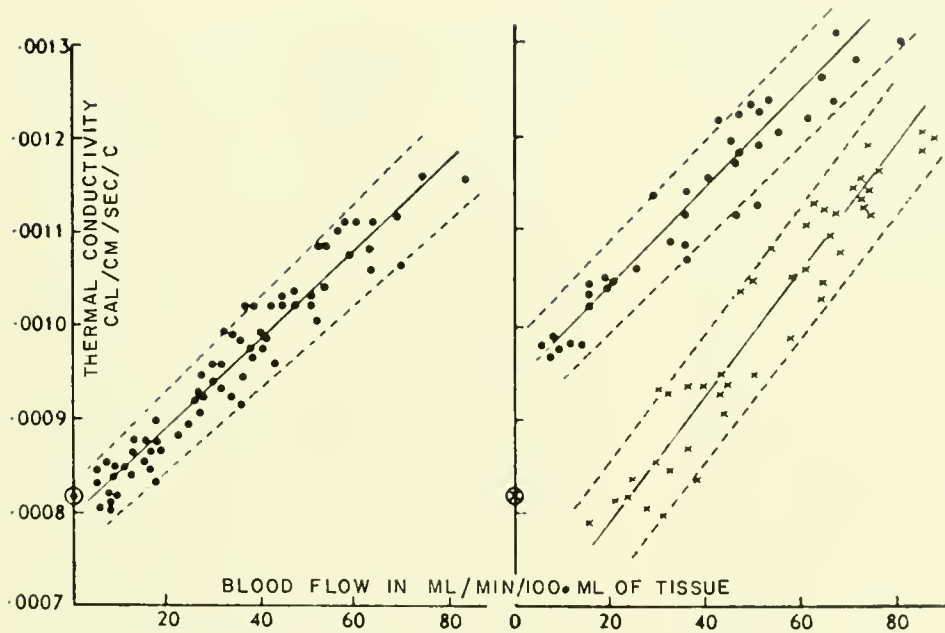


FIG. 10. The relationship between effective thermal conductivity of the skin and blood flow in the fingers. The three curves are for different subjects. The points for zero flow (circled) were obtained by occlusion of the flow by a cuff on the proximal phalanx, while the other data for low flows were obtained by vasoconstriction in response to cold. [From Burton (21).]

state, a higher temperature above the skin than the other, 'ring' coil. The difference of temperature between the two coils is registered directly by the deflection of the galvanometer of the bridge." [Burton (21).]

Hensel's device consists of a round plexiglass plate on which the hot and cold thermojunctions are placed at a distance of a few centimeters. The units can be applied to finger tips and the conductivity increment obtained with changes of blood flow can be checked by the venous occlusion technique. Burton's results on three subjects show linear relationships (fig. 10). However, in the ischemic state λ varies significantly from subject to subject so that a general calibration cannot be used.

A similar device to apply on the brain surface in animal experiments has been designed by Kanzow (58a). In his unit heat is directly applied by diathermy to the brain tissue, and the temperature difference between the heated area and the unheated control area is measured by thermocouples. This device

shows that a linear relationship between λ and blood flow exists, providing the electrical resistance of the tissue does not change. Kanzow claims that λ -changes occurring with changes in blood content within the tissue can be detected from readings of tissue resistance, thereby helping to avoid errors in blood flow estimations.

Thermocouples can be replaced by thermistors which are placed in Courmand catheter tips or in glass cannulas used for blood flow measurements in larger vessels (23, 28, 30, 36, 61, 67, 76, 78, 84, 89). The chief advantage of such units is their small size. However, this type of device does not distinguish backward from forward flow, and quantitative measurement of blood flow is not possible with it since the diameter of the vessel is not controlled. Even with measurements on arteries cannulated with glass tubes with imbedded thermistors the results are doubtful, since the velocity profile of the blood is not uniform. Also, recordings of flow pulses are distorted because of the low frequency response of such units.

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II. Admixing methods for measurement of regional blood flow

WILHELM LOCHNER

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BLOOD TISSUE EXCHANGE METHODS

Nitrous Oxide Method

MEASUREMENT OF CEREBRAL BLOOD FLOW. The nitrous oxide method for determination of cerebral blood flow was developed by Kety & Schmidt (20, 22) in 1945. Since then it has become a standard method for determinations in man of both cerebral and coronary blood flow, especially because extensive operative procedures can be avoided. The nitrous oxide method makes use of Fick's principle of blood flow estimation. The test substance, nitrous oxide, is an easily diffusible, inert gas which diffuses into the tissues fast enough to allow equilibrium between gas tensions in tissue and venous capillaries. With a known partition coefficient of the gas, and under the assumption that equilibrium between tissue and blood is

reached, the amount of test substance taken up by 100 g of tissue can be calculated (21). Simultaneous measurement of arteriovenous nitrous oxide difference then permits calculation of the blood flow per minute per 100 g of tissue. Applying Fick's principle, the formula (22) is:

$$CBF = \frac{100 \cdot V_u \cdot S}{\int_0^u (A - V) dt}$$

wherein

A = arterial N_2O -concentration

V = venous N_2O -concentration

S = partition coefficient for N_2O between blood and tissue

V_u = venous N_2O concentration after equilibrium reached in tissue during time u

CBF = cerebral blood flow per 100 g brain tissue per min

The procedure of measurement is as follows: The patient breathes a gas mixture of oxygen, nitrogen and 15 per cent nitrous oxide over a period of 10 min (time u). During this time, five consecutive blood samples are taken simultaneously from the internal jugular vein and from a peripheral artery. The samples must be collected under anaerobic conditions. They are analyzed for N_2O according to the method of Orcut & Waters (33). [See also Kety (23).] Figure 1 shows arterial and venous time-concentration curves of nitrous oxide in a typical determination. As can be seen from the figure, ten blood samples have to be analyzed, an undesirable feature of the method. A modification of this method has been proposed by Scheinberg & Stead (38) and by Bernsmeier & Siemons (3). Intermittent sampling is replaced by continuous sampling of only two probes, one arterial

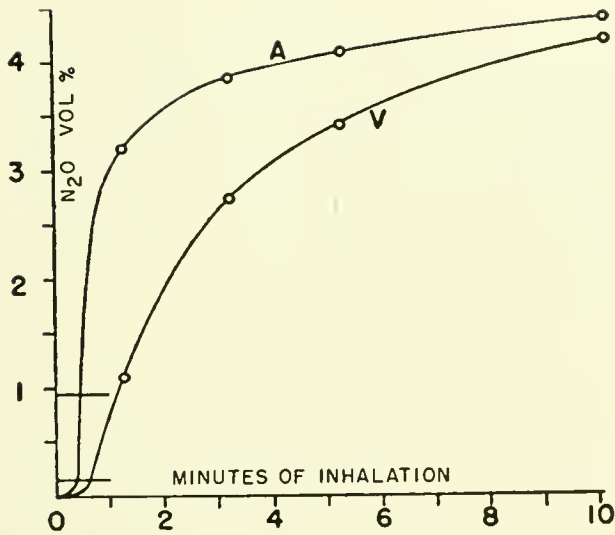


FIG. 1. Typical arterial (A) and internal jugular (V) curves of N_2O concentration during a 10-min period of inhalation of 15% N_2O . [From Kety & Schmidt (22).]

and one venous, during the measuring period of 10 min. The advantages of this modification are seen in the fact that *a*) only one person is needed for taking the samples, *b*) less blood is taken from the patient, and *c*) the number of gas analyses is reduced from ten to three (25). The modified method yields results identical with those obtained with the original method. However, Kety (24) prefers his primary procedure of intermittent sampling since he believes that the course of arterial and venous time concentration curves allows an estimation of the volume of blood from extracranial vessels which has been intermixed with cerebral blood flow. This point is of general importance and will be briefly discussed here. The main premise is that representative mixed venous blood of the brain is obtained for measurement of gas concentrations. It is not necessary for the total blood flow of the organ to pass through one vein. However, it is required that the concentration of test substance be equal in all veins. Samplings from the bulbous cranialis of the internal jugular vein have proved to be fairly free of extracranial blood. Shenkin *et al.* (40) estimate a maximal admixture of 2 to 3 per cent. For proper use of the partition coefficient of nitrous oxide in blood and tissue—its value for cerebral tissue is about one—it is important that concentration equilibrium between tissue and blood has been reached. Even small differences between arterial and venous concentration lead to errors, as Sapiirstein & Ogden (37) have shown. This fact would seem to make the original intermittent sampling technique the method

of choice. Simultaneous measurements of cerebral blood flow in monkeys by the nitrous oxide method and by bubble flowmeter show good agreement (22).

MEASUREMENT OF CORONARY BLOOD FLOW. Soon after the introduction of the nitrous oxide method for the determination of cerebral blood flow, the method was used to measure coronary blood flow (6, 7, 12). The blood of the coronary sinus is representative of the left ventricular coronary flow, and since the improvement of catheterization technique has made it possible to sample blood from the coronary sinus, the nitrous oxide method can be applied successfully in man (4). In coronary blood flow experiments on dogs, Gregg and co-workers (14) found good agreement between values obtained by use of the rotameter and the nitrous oxide method. A series of investigations has been undertaken using the desaturation course of nitrous oxide. The results were similar to those obtained by the method of saturation [Goodale & Hakel (11) and Barger *et al.* (2)].

Other Test Substances

Radioactive krypton 85 has been proposed by Lassen & Munck (26, 29) for use in the determination of cerebral blood flow. The procedure is very similar to that of the nitrous oxide method. The application of krypton 85, although it allows greater accuracy, has the disadvantage of requiring special instrumentation and the risk to the patient of radiation exposure. Munck & Lassen have recommended that internal jugular blood should be sampled bilaterally because concentration of the test substance may differ in the two veins. Blood flow is then calculated twice and the mean is taken. Since gaseous test substances require special care in sampling and storing of blood, and since the analyses are time consuming and difficult under conditions of gaseous anesthesia, Huckabee (17) proposed the use of 4-aminoantipyrine. This is a nonvolatile, biologically inert substance, which diffuses rapidly from blood into tissue fluid, and is relatively easy to measure. [See also (14), (19), (18).]

TEST-SUBSTANCE DILUTION METHODS

These also employ the Fick principle. Blood flow through an organ is determined from the ratio of the amount of injected test substance to its concentration in the effluent blood. In case there is, for any reason, some of the indicator substance in the blood at the

time of injection, the arteriovenous difference in concentration of the substance may be substituted. A rapid injection of the substance into the blood stream is used. This procedure was originally developed to determine cardiac output (15). Description of the method and its theoretical implications have been given by Hamilton (14a) and Zierler (41). For application of the method to blood flow of any organ, the general formula holds:

$$F = \frac{m}{\int_0^{\infty} c(t) dt}$$

wherein

- F = blood flow
- C = concentration of test substance in the effluent blood
- t = time elapsing during passage of test substance
- m = amount of test substance injected.

Measurement of Coronary Blood Flow

Hirche & Lochner (16) have adapted the method to determine coronary blood flow in anesthetized dogs. A main branch of the left coronary artery (descending branch or circumflex branch) and the coronary sinus are catheterized. Cardiogreen (5) is used as the test substance. For continuous measurement of dye concentration, the mixed venous blood of the heart muscle is drawn by a pump from the sinus catheter through a cuvette photometer (27). When the dye is injected either into the descending or circumflex branch, time-concentration curves of equal area are obtained. The sinus catheter should be placed close to the outflow. Hirche and Lochner have concluded that the method gives values of the sinus outflow only. Since about 10 per cent of left coronary artery blood may not be returned by the coronary sinus, and therefore a proportionate amount of dye does not appear with this venous outflow, 10 per cent of the calculated blood flow must be subtracted for quantitative measurement. Values obtained with this method are in agreement with those measured by other methods reported in the literature. The measurements can be repeated in intervals of 1 to 2 min and in practically unlimited number.

Measurement of Cerebral Blood Flow (10, 22, 30-32, 39)

The human brain receives nearly all of its blood through two vertebral and two internal carotid ar-

teries. The blood leaves the brain through two main veins, the two internal jugulars. It would be theoretically justified to apply the test-substance injection method if, following injection into one arterial branch, one could obtain identical time-concentration curves in all veins. This would indicate that the mixing of the test substance in all brain vessels was complete. However, the results described below show that such mixing is not obtained. Injection of test substance into one internal carotid yields three distinct types of time-concentration curves in the separate internal jugular veins.

1) The test substance may appear only on one side. This finding would allow the conclusion that blood flow of only one hemisphere is measured. 2) The concentration curves may be identical in both internal jugular veins. This would correspond to the ideal case where blood flow through the brain as a whole is measured. 3) Most frequently, however, it happens that although the dye appears in both internal jugular veins, the concentrations differ to a high degree.

It is proposed to average the blood flow values obtained from both time-concentration curves. However, it seems questionable whether this procedure yields accurate quantitative values for brain blood flow. Using the test-substance injection method, Shenkin *et al.* (40) have studied the "dynamic anatomy of the brain," mainly to test the validity of the nitrous oxide method. The advantage of the latter lies in the fact that all cerebral arteries show the same concentrations of nitrous oxide at any period of time. In spite of this, the measurements made from the internal jugular veins sometimes do not give identical values (29). When the method of sudden and short injection of the test substance is applied, the interpretation is much more complicated. Even in the simple case of two identical time-concentration curves cerebral blood flow cannot be correctly estimated, since not all the test substance appears at the internal jugular measuring points. About 22 per cent of the blood flow through the external jugular vein is derived from internal carotid blood, as Shenkin has shown. One cannot assume that the test substance leaving the brain via the external jugular vein has mixed thoroughly with all the blood passing the brain. The difference between two time-concentration curves from the internal jugular veins speaks against it. This means that accurate measurement of cerebral blood flow cannot be obtained with the test-substance injection method, even when concentration curves of both internal jugular veins are recorded.

Measurement of Flow in Other Organs

The blood flow of the extremities has been measured in man using the test-substance dilution method [Andres *et al.* (1)] and in the isolated kidney by Lochner & Ochwaldt (28). Piiper (35, 36) determined the site of main resistance to flow in the vascular bed of the lungs by injection technique, and also the site of capillaries in the vascular volume of the isolated lungs.

Measurement of Flow in a Blood Vessel Without Interposing an Organ

In the procedures described above the perfusion of an organ was measured. The organ served as a mixing chamber, and a reliable time-concentration curve of the test substance was obtained as it left the organ.

Peterson *et al.* (34), on the other hand, have developed a method to measure the outflow of the left ventricle which does not involve mixing of the blood and indicator substance within the heart. The indicator is injected into the root of the aorta and its concentration is measured in an artery. In the same way, Grace *et al.* (13) have measured flow in the thoracic aorta. Whereas the above-mentioned two groups used dyes, Frank *et al.* (8) used cold solutions. Fronek & Ganz (9), using cold injections, were able to measure blood flow in individual small vessels by placing the injection and recording sites in close proximity. Since laminary flow is dominant in the blood vessels, special care must be taken to achieve complete mixing of the test substance with the blood. This can be done by choosing a proper diameter and arrangement of holes at the tip of the injection catheter or needle.

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III. Flowmeters: their theory, construction, and operation

E. WETTERER

Ultrasonic Flowmeters
Traveling Markers
Miscellaneous Methods

CONTENTS

Flowmeters Based on the Registration of Pressure Differences
The Rotameter
The Electroturbinometer
Bristle and Pendulum Flowmeters
Methods Based on the Electromagnetic-Induction Principle

THE PURPOSE of most registrations of blood flow is the recording of the fluid volume passing the cross section per unit of time. The flowmeter used will therefore be calibrated in terms of rate of volume flow. In ad-

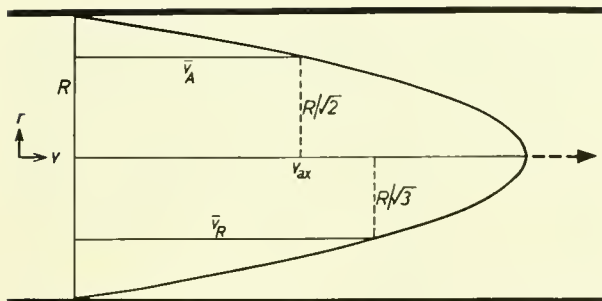


FIG 1. Parabolic velocity profile according to Poiseuille's law in steady laminar flow. For explanation see text.

dition, the fluid velocity at particular points within the cross section may be of interest, especially in hydrodynamic studies. In these cases, the flowmeter is calibrated in terms of fluid velocity.

Since different flow types occur in the circulation, and even in the same blood vessel, any calibration in terms of flow rate presupposes an examination of the dependence of flowmeter response on the velocity distribution over the cross section.

In case of steady laminar flow, the velocity distribution is in the form of a paraboloid, the profile of which is represented in figure 1. If v is the velocity at the distance r from the axis and R is the radius of the tube, then we have, according to Poiseuille's law:

$$v = K(R^2 - r^2) \quad (1)$$

where $K = (\Delta P / \Delta x) \cdot (1 / 4\mu)$; $\Delta P / \Delta x$ = pressure gradient in axial direction; μ = viscosity of the fluid. The maximum velocity is at the axis where $r = 0$:

$$v_{0x} = KR^2 \quad (2)$$

while the lamina adhering to the wall ($r = R$) is at rest. When equation 1 is integrated over the cross-sectional area, the flow rate \dot{Q} is obtained:

$$\dot{Q} = 2\pi \int_0^R vr \cdot dr = \frac{1}{2} K \pi R^4 \quad (3)$$

The average velocity taken over the cross-sectional area is \bar{v}_A :

$$\bar{v}_A = \frac{\dot{Q}}{R^2 \pi} = \frac{1}{2} KR^2 \quad (4)$$

It follows from equations 1 and 4 that the fluid lamina moving at the velocity \bar{v}_A is at a distance of $R/\sqrt{2}$ from the axis.

With respect to the performance of some flowmeters, the velocity \bar{v}_R averaged over the radius or

diameter must also be considered:

$$\bar{v}_R = \frac{1}{R} \int_0^R v \cdot dr = \frac{2}{3} KR^2 \quad (5)$$

From equations 2, 4 and 5 we obtain the ratios:

$$v_{0x} : \bar{v}_A = 2 : 1 \quad (6)$$

$$\bar{v}_R : \bar{v}_A = 4 : 3 \quad (7)$$

If the critical Reynolds number is exceeded, the flow becomes turbulent; the profile of the net forward velocities is then flattened and approaches, with increasing turbulence, complete flatness. Other conditions, which will be mentioned below, may also give rise to a flattening of this profile. In the extreme case of complete flatness, all fluid particles are moving uniformly at the net forward velocity \bar{v}_A .

Now we may consider how different flowmeter types will behave when the velocity profile changes from the parabolic shape to complete flatness. A flowmeter which responds to the axial flow only has a relatively high sensitivity when the flow profile is parabolic, since, according to equation 6, $v_{0x} : \bar{v}_A = 2 : 1$. When the profile is completely flat, the axial velocity will be as high as the velocity at any other point so that the sensitivity in terms of flow rate is now reduced by 50 per cent from the case of a parabolic profile. In theory, this loss in sensitivity could be avoided by placing the flow-sensing element at a distance of $R/\sqrt{2}$ from the axis where, in the parabolic profile, the local velocity equals \bar{v}_A as discussed above.

If the response of a flowmeter is determined by the sum of the velocities at all points covering the diameter or the radius, this response is proportional to \bar{v}_R . The sensitivity in terms of flow rate will then decrease by 25 per cent when the profile changes from the parabolic shape to complete flatness since $\bar{v}_R : \bar{v}_A = 4 : 3$. It is obvious that the sensitivity of those flowmeters which respond primarily to the velocity \bar{v}_A averaged over the cross-sectional area is independent of the velocity profile. The conditions are more complicated if the flowmeter's response to the fluid velocity is not linear, as is the case with most devices based on hydrodynamic principles.

Particular conditions are given in the inlet section of a tube into which fluid is driven from a larger reservoir as is the case in the trunks of the aorta and pulmonary artery. At the entrance of such a tube the velocity profile is flat except in a small marginal zone where a thin boundary layer showing a steep radial velocity gradient exists. When the site of observation

is shifted along the tube, the boundary layer is found to increase in thickness and will finally occupy the whole cross section forming the parabolic profile of laminar flow, provided that the Reynolds number is below the critical value. The so-called inlet length, i.e., the distance between the beginning of the tube and the site where a parabolic profile is just established, can be calculated [see McDonald (93)]. If the Reynolds number is above the critical value, the inlet length is the distance between the beginning of the tube and the site where turbulence is fully developed; this inlet length, too, is calculable and will be much shorter than for laminar flow. Under both conditions, however, the velocity profiles in the trunks of the aorta and pulmonary artery are almost flat so that the use of flowmeters involves no essential difficulties regarding the velocity profile, unless the flow type is altered by abnormalities such as valvular stenosis. Some flattening of the velocity profile also occurs when the fluid is streaming from a wider into a narrower tube segment through a conical intermediate section. This effect may be utilized to improve the performance of some flowmeters regarding the dependence on the velocity profile.

The pulsatile flow in peripheral arteries is characterized by phase differences between the layers oscillating at various distances from the axis. Generally, the oscillation of the layers near the axis shows a phase lag in relation to the more marginal zones. While at low frequencies of the flow oscillations the phase lag increases continuously from the margin toward the axis, the inner zones will swing closer in phase to each other when the frequency is raised. At high frequencies, a wide central column of fluid will oscillate uniformly, and the profile of oscillation will approach flatness (93). It is obvious that flowmeters which respond to v_{ax} or to \bar{v}_R are showing, in case of pulsatile flow in peripheral arteries, errors not only in amplitude but also in phase, as will be discussed below with special reference to the pendulum and bristle flowmeters. Only flowmeters responding to \bar{v}_A will deliver records free from such distortions.

Another point of view is the consideration of the frequency characteristics which a flowmeter must possess to obtain adequate recordings of pulsatile flow. The highest frequencies occurring in the central flow pulse of the dog under physiological conditions amount to 50 to 100 cycles per sec (cps). For recording the main features of the central pulse a frequency response up to about 50 cps is sufficient (34, 35). In larger animals and in man the upper frequency limit may be somewhat lower, but it is remarkably

higher in small animals. In case of mechanical pickup systems capable of vibrating, the natural frequency should be at least double the highest frequency to be recorded when the system is critically damped. In an electrical system based on a carrier-frequency procedure, the carrier frequency must be high enough to reach an adequate band width. Further details will be discussed in the description of the various flowmeters.

The application of flowmeters to the circulation usually involves a local alteration of the flow conditions resulting from insertion of a cannula, from placing an obstacle to flow within the streaming fluid, from constriction of the blood vessel from outside, or at least from surrounding the vessel with a rigid sleeve. A slight constriction extended over a short length generally will not give rise to objectionable changes of the flow conditions. The frictional drop of the mean pressure is often used as a measure of the impediment to flow caused by the flowmeter. It is obvious that the pressure drop should be small as compared to the absolute pressure level. This criterion alone, however, is not sufficient, since an arterial segment which contains an obstacle or is made rigid by an inserted cannula or a surrounding sleeve can change the hemodynamic conditions by causing pulse-wave reflections even if there is no remarkable drop of the mean pressure. For this reason, the length of a rigid segment should not exceed 1 cm (93).

FLOWMETERS BASED ON THE REGISTRATION OF PRESSURE DIFFERENCES

When a liquid flows through a tube, a pressure difference between two points along the tube may be generated by friction and by mass inertia. Whereas the influence of friction results in a pressure difference proportional to the flow velocity, the effect of inertia is causally connected with flow acceleration. Two kinds of acceleration, convective and local, have to be considered. Convective acceleration (dv/dx = change in velocity along the axial direction) occurs in steady as well as in pulsatile flow as a result of variation in cross-sectional area of the tube or by an arrangement which causes a locally circumscribed stagnation of the fluid or a change of the flow direction. According to Bernoulli's theorem, pressure differences due to convective acceleration are proportional to the square of flow velocity. Local acceleration (dv/dt = velocity change in time, observable at a single point, i.e.,

“locally”) takes place only when the flow rate is changing in time. Pressure differences between two points which are caused by local acceleration are proportional to the differential quotient of the flow velocity, to the fluid's density, and to the distance between both points. Thus, we have, according to Frank (39), the following equation:

$$P_1 - P_2 = \underbrace{C_1 v}_I + \underbrace{C_2 v^2}_{II} + \underbrace{C_3 \frac{dv}{dt}}_{III} \quad (8)$$

where P_1 and P_2 = instantaneous pressures at two different points; v = instantaneous flow velocity; t = time; C_1 , C_2 , and C_3 = coefficients; I = frictional term; II = inertia term due to convective acceleration (Bernoulli); III = inertia term due to local acceleration. The pressure difference ($P_1 - P_2$) is recorded by a suitable differential manometer (see below). In most experimental cases, the coefficients are determined by practical calibration although they are, under certain conditions, calculable from the tube dimensions and from density and viscosity, respectively, of the fluid. If, instead of the linear velocity v , the rate of volume flow is used in equation 8, then C_3 is equivalent to the so-called effective mass M' (Frank):

$$M' = k \cdot \frac{\rho L}{A} \quad (9)$$

where ρ = density of fluid, L and A = length and cross-sectional area, respectively, of the fluid column contained in the tube between both points and k = correction factor for velocity distribution within this column; $k = 1.0$ if the velocity profile is flat [see (46, 48)]. As Ranke (107) pointed out, equation 8 must be regarded as an approximation, since the coefficients change with the Reynolds number for the flow and further terms may have to be taken into account.

The properties of most differential-pressure flowmeters which respond to pulsatile flow are dependent upon the three terms of equation 8, although, for certain models, one or two terms may play a dominating role. If only mean flow is recorded, term III can be ignored; nevertheless, a great effective mass (coefficient C_3) should be avoided because it alters hemodynamic conditions in the case of pulsatile flow [cf McDonald (93)]. If the tube diameter is large, as in great central vessels, term I usually has little significance as compared to term II.

If the pressure difference is generated mainly by friction as in figure 2, the device must be constructed in such a way that the resulting pressure drop will



FIG. 2. Friction device. UPO, DPO = lateral openings upstream and downstream from the constriction for connection with differential manometer. [From Green (50).]

not be so great as to disturb the physiological conditions. A friction device consisting of a long, narrow plastic tube inserted into a blood vessel was applied by Ueno & Takenata (129) for recording the mean flow; the pressure drop was measured by a rolling manometer. It seems likely that it interferes with normal blood flow.

An older method may be mentioned here. In 1935, Green *et al.* (53) tried to estimate the systolic and diastolic coronary-artery flow from the pressure difference between the aorta and a peripheral coronary branch. There is, however, no simple relationship between these magnitudes, because waves traveling in elastic tubes are concerned. Therefore, the method was abandoned [cf Gregg's criticism (54) and Chapter 7, vol. 1, this *Handbook*].

The principle of the Venturi meters is based on the generation of convective acceleration by a variation in the cross-sectional area of a tube (Venturi 1797; Herschel 1887). As shown in figure 3, the fluid has to move from a wider into a narrower tube segment. According to the continuity law, equal quantities of an incompressible fluid must pass each cross section of a rigid tube during the same time interval. The fluid's linear velocity is therefore augmented in the narrow segment so that here the kinetic energy is increased and the lateral pressure is decreased. This results in a pressure difference between UPO and DPO in figure 3, which is proportional to the square of the average flow velocity (term II in equation 8). If the tube widens again downstream from DPO to the same cross-sectional area as before, the former pressure is restored. The additional influence of friction will augment the pressure difference between both points (term I); this part of the pressure drop, of course, is not reversible by rewidening of the tube. When the rate of volume flow is changing in time, a third kind of pressure difference corresponding to term III appears which should be kept minimal because it distorts the records. Devisers of such flowmeters often failed to take this source of error into consideration. Lauber's Venturi cannula (87), for instance, was criticized by Frank (42) because its



FIG. 3. Venturimeter of original type. [From Green (50).]

manometer connections were very distant from each other. The aortic flow records obtained with this cannula therefore represented acceleration curves rather than velocity curves. A detailed polemic was carried out on this point by Frank (41, 42) on the one side and by Broemser (16) and Ranke (107) on the other. To minimize the distortions, the distance between both manometer connections (length L in equation 9) must be as small as possible. In contrast to a widely held opinion, the distorting effect of term III cannot be detected by comparing the directly measured mean flow with mean pulsatile flow determined by planimetry of the recorded curves. This is true because when areas are determined by the planimeter, the distortions generated during flow acceleration may be compensated for by opposite distortions generated during flow deceleration. An analytical correction of the records would be feasible, but very difficult. The best way, therefore, is to keep C_3 minimal by appropriate construction of the flowmeter. Similar considerations apply also to Pitot tubes (see below).

Venturi tubes like those of figure 3 are used relatively seldom. The cannulae of de Burgh Daly (20) and of Lauber (87) may be mentioned here. Lawson & Holt (88) modified Daly's method.

The Venturi principle is applicable also to other designs. Figure 4 shows the effect of an inflection of the tube wall on the streamlines. In case of such an inflection of small length, the point at which the streamlines run closest to each other is not situated at the tip of the inflection, but somewhat downstream from it. This means that the fluid's linear velocity is higher and the lateral pressure is lower on the downstream side than on the upstream side of an inflection or constriction. Thus a pressure difference corresponding to term II is generated between two points situated upstream and downstream from a nearby constriction even if the tube's cross sections are equal at both points.

Broemser (15) and Reissinger (109) in 1928, making use of this effect, constructed an instrument which proved appropriate for recording pulsatile flow in the ascending aorta (fig. 5). The advantages of this cannula consist in the very short distance between the

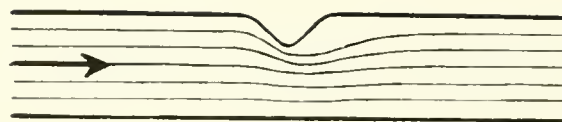


FIG. 4. Deviation of streamlines caused by an inflection of the wall. [From Reissinger (109).]

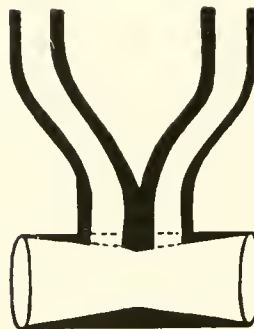


FIG. 5. Cannula of Broemser and Reissinger. [From Reissinger (109).]

lateral openings and in their symmetrical arrangement which provides equal sensitivity to forward and backward flow. The optimal inflection angle between tube axis and wall was found to be 7 to 8°; by using this angle, sufficient sensitivity is achieved and no eddies occur even at the highest physiological flow velocities. Since the planes of the lateral openings are not parallel with the vessel axis, an additional Pitot effect (see below) may be involved.

Nilsson & Kramer (97) in 1954 developed a Venturi meter according to the aforementioned principles for the registration of the pulsatile flow in the intrathoracic vena cava. Steady and oscillatory flow calibrations showed that, for this device, the terms I and III are of subordinate significance.

The orifice flowmeter of Gregg & Green (55) [cf Green (50) and Gregg (54)] is also based on the Venturi principle. The pressure difference is generated by an opening (= orifice) in a thin disk placed across the stream (see fig. 6). Lateral manometer connections are arranged upstream and downstream from the disk at distances equal to the tube radius. As seen from figure 6, the streamlines converge downstream from the orifice so that there is a point at which the pressure reaches a minimum as described above. Due to its symmetrical arrangement, this device has equal sensitivities to forward and backward flow. The size of the orifice can be adjusted during the experiments either by substituting disks of different orifice diameters through a slot in the cannula wall or, according to a modification devised by Shipley *et al.* (120), it can be altered from the outside by means of a stud screw, the rounded end of which protrudes into the

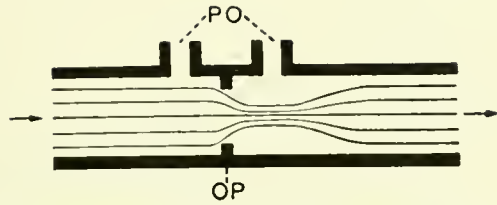


FIG. 6. Principle of orifice flowmeter of Gregg and Green. *PO*, connections to differential manometer; *OP*, orifice plate. [From Green (50).]

cannula lumen. Details of construction, as well as the connection of the orifice-meter cannula to the differential manometer, are shown in figure 7. The rubber membrane of the manometer, to which the mirror is attached, bulges under the action of pressure differences between its two sides, while it is insensitive to the absolute pressure. The steady-flow calibration curve is virtually quadratic if saline solution is used. When blood is used, the effect of term I is noticeable. The natural frequency of the differential manometer amounts to 50 to 70 cps or more (54). It is difficult to judge the effect of term III on the records of pulsatile flow; the coefficients of equation 8, including C_3 , vary with the cannula and orifice diameter. Arterial flow curves recorded with the orifice meter, particularly those of the femoral, axillary, and carotid arteries (120), might suggest that the contour of the systolic flow peak and the registered backflow phase could be markedly affected by term III, although arterial flow patterns are widely variable for physiological reasons, as McDonald (93) discusses in detail. The applicability of the orifice meter to veins is limited because of its frictional pressure drop.

Schroeder's differential - pressure flowmeter ("Druckdifferentialstromuhr") (119) may be regarded as a further developmental stage, obtained by new technical means, of Broemser's differential sphygmograph (see below). Schroeder designed his instrument, which is shown in figure 8, for application on unopened carotid and femoral loops of conscious dogs. In a special compartment (*C*), the artery (*A*) is compressed by a screw device (*S*) so that its wall is relaxed. Two rubber diaphragms (D_1 , D_2), arranged at the bottom of the compartment, are in direct contact with the skin surrounding the vessel, one diaphragm is placed at an upstream vessel segment, the other at a downstream segment. Each diaphragm covers a water-filled chamber (Ch_1 , Ch_2), and can transmit the pressures from both vessel segments into these chambers. Due to the compression of the vessel, its skin and wall tissues are deformed so that the vessel

lumen is narrowed toward the middle of the compartment; the slight constriction gives rise to a flow-related pressure difference between the two vessel segments, which is detected by a thin metal membrane (M_1) interposed between the chambers and is transferred by a lever (*L*) to an air-pressure nozzle amplifier (NA_1) for optical manometer registration. By two other membranes (M_2 , M_3) connected to similar air-pressure amplifiers (NA_2 , NA_3), the pressure of each chamber is picked up, and the sum of both pressures is optically recorded by an adding manometer. In this way, the difference between the pressures (related to the blood flow) and their sum (related to the blood pressure) are recorded simultaneously. The steady-flow calibration curve is almost quadratic; it is corrected automatically by an optical linearizing device. Distortions due to term III of equation 8 are reduced by attaching an air chamber to the differential-pressure air-transmission system. Although some mechanical functions of this design may require further theoretical clarification, its records of pulsatile arterial flow and pressure resemble to a surprisingly high degree those obtained by other well-recognized instruments.

Two other devices may be mentioned here for re-

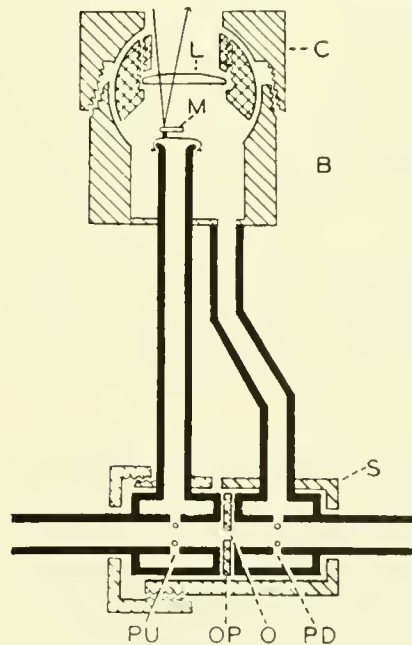


FIG. 7. Construction of orifice flowmeter and differential manometer. *OP*, orifice plate; *O*, orifice; *PU* and *PD*, upstream and downstream connections to manometer. *S*, shell; *B*, base; *C*, cap of manometer. *L*, lens, carried by a ball. *M*, mirror attached to rubber diaphragm of manometer. [From Green (50).]

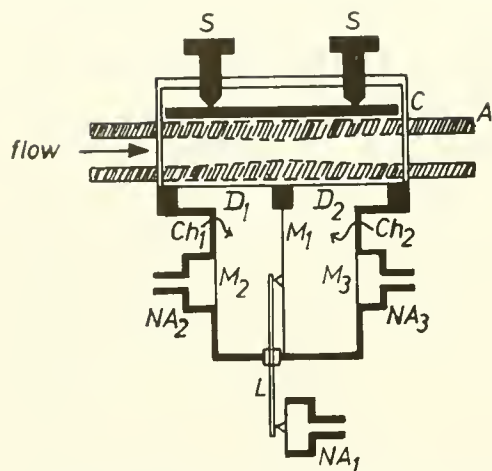


FIG. 8. Differential-pressure flowmeter of Schroeder (119) for application on skin-coated arterial loops. For description see text.

cording mean flow. A Venturi cannula in connection with a differential water manometer, for application to abdominal arteries, was used by Wagoner & Livingston (131). Wretling (138), modifying a plan by Stephenson (1948), carefully designed a meter for mean flow in the ascending aorta of the cat. As figure 9 shows, the blood streaming from A to B passes a constriction (D) of small length which causes a pressure drop of a few mm Hg. Pulsations in the differential manometer (G) records are eliminated by expanding chambers (C, E) at the upstream and downstream side of the constriction; within these chambers, pulsating blood columns rise to different mean levels corresponding to the pressure difference which is necessary to drive the mean blood flow through the constriction. The tops of the two chambers are connected to each other by an air-filled tube (F) which acts as an elastic bypass transmitting a part of flow pulsations from the central to the peripheral end of the meter.

The principle of Pitot flowmeters (1728–1732) consists in the measurement of the hydrodynamic increment in pressure which is generated by the locally circumscribed stagnation of a small part of the streaming fluid. For this purpose, a thin tube, the opening of which faces upstream, is placed in the fluid. The difference between the pressure exerted on that opening (“end” or “total” pressure) and the “lateral” (or “static”) pressure is indicated by a differential manometer. The opening which picks up the lateral pressure may be placed in the wall (fig. 10) or near the opening facing upstream (fig. 11). In other devices, two thin tubes are inserted, with one

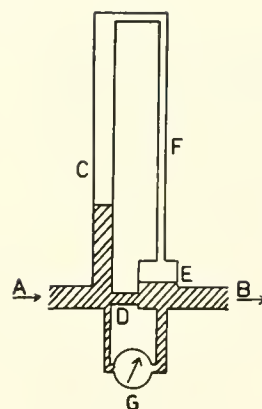


FIG. 9. Flowmeter of Wretling for ascending aorta of cat. For description see text. [From Wretling (138).]

opening upstream and the other downstream (fig. 12); the pressure difference is greater with this design because suction is effected at the downstream opening by eddy formation. This arrangement also offers the advantage that almost equal physical conditions can be provided to measure forward and reverse flow. If equation 8 is applied to Pitot meters, v of term II is not the average velocity of the fluid, but the velocity of that small bundle of streamlines which hits the opening facing upstream. This is an advantage because it offers the possibility of using Pitot meters like those illustrated in figures 10 to 12 as probes which can be shifted along the tube radius in order to measure, point by point, the hydrodynamic pressure distribution between the axis and the wall. Thus, the velocity profile is determinable for hydraulic investigations of theoretical and practical interest [Müller (95)]. If, on the other hand, the average flow velocity is to be detected by Pitot meters, errors resulting from changes of the velocity profile have to be taken into account. If the flow is pulsatile, term III of equation 8 requires special consideration.

Prandtl's tube (fig. 11) is a modification of the Pitot meter; the openings lie at the surface of a probe which is placed in the streaming fluid. This device minimizes eddy formation.

The construction of most Pitot meters applied in cardiovascular physiology can be deduced from one of the types shown in figure 10 to 12. Aortic flow was recorded in 1899 with Frank's (36) double-lumen catheter which was introduced through the carotid artery. Other Pitot devices were used by Baxter & Pearce (4) and by Jameson (67) for recording the pulmonary artery flow, by Johnson & Wiggers (70) for recording the coronary sinus outflow, and by Eckstein *et al.* (26) for recording the vena cava flow.

“Torpedo”-shaped Pitot meters offering low resistance to flow were built in 1953 by Brecher (8) and

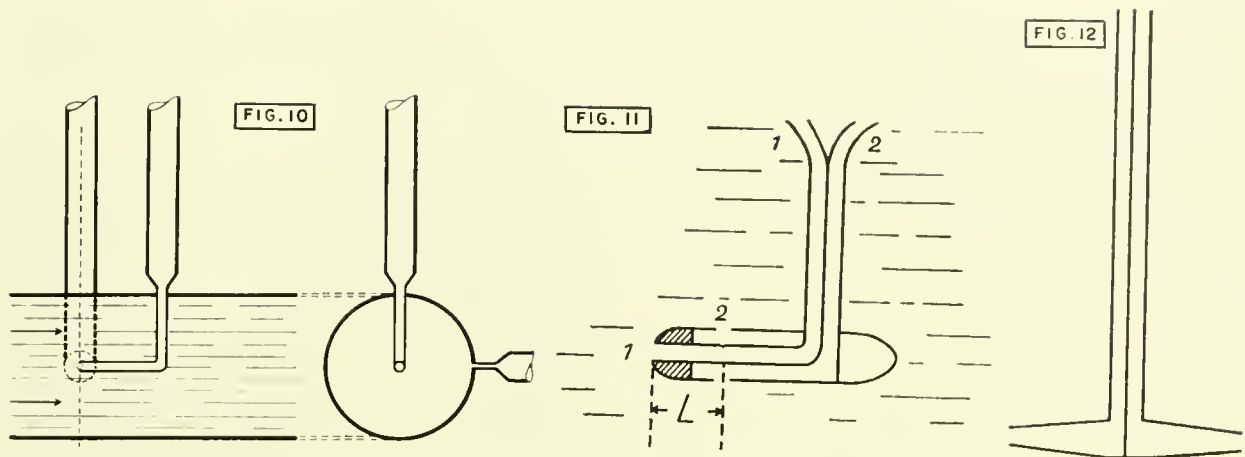


FIG. 10. Pitot meter with asymmetrical pressure taps, one facing upstream, the other arranged to measure lateral pressure. [From Müller (95).]

FIG. 11. Prandtl's tube, based on the Pitot principle. 1, upstream facing pressure tap. 2, lateral pressure tap. L , distance between 1 and 2. [From Hardung (57).]

FIG. 12. Pitot meter with symmetrical pressure taps facing upstream and downstream. [From Müller (95).]

by Mixer (94). Brecher's device (fig. 13), designed for introduction into the superior vena cava from the jugular vein, consists of a rigid three-tube catheter at the tip of which a streamlined lead "torpedo" is attached. It contains the upstream and downstream facing ends of the differential-manometer tubes U and D while the longer tube A , serving to detect the pressure in the right atrium, is connected to a separate manometer. Tube A can be moved along U and D by working an outside handle; in this way, springs are expanded to form a basket (dashed lines in fig. 13) around the torpedo in order to keep it centered in a vessel of constant diameter. Mixer's torpedo is placed in a metal tube for direct insertion into a large vein.

A promising attempt to improve the performance of the Pitot meter was recently made by Bretschneider (13), who realized the difficulties involved in the estimation of the average velocity from the velocity of a small bundle of streamlines. He placed the opening facing upstream at a point where the local fluid velocity equals the average velocity for both laminar and turbulent flow. Theoretically, this point is situated at a distance of about $0.7 R$ from the tube axis, or $0.3 R$ from the wall, i.e., $R/\sqrt{2}$. This arrangement, however, is impracticable if the lumen diameter is 6 mm or less. In such cases a greater relative distance from the wall (0.4 – $0.6 R$) has to be chosen. Errors due to such malposition are substantially reduced by using a flow cannula with a conical inlet section which flattens the velocity profile. Thus Bretschneider obtained an average flow calibration curve which is unaffected

within a wide range by changes of viscosity (water-blood), by changes of the flow type (laminar-turbulent), and even by changes of the velocity profile caused by flow pulsations, provided the flow remains unidirectional. Using his modification of the Pitot meter, he constructed a catheter-tip cannula for recording the coronary-sinus outflow as well as another cannula for measuring the pump output in extracorporeal-circulation devices. It seems possible to combine these advantages with the arrangement described by Hardung (see below) which avoids distortions caused by local acceleration.

Besides the aforementioned Pitot types, there is an older modification used by Cybulski (19). As shown in figure 14, the sharp angle in the tube causes a sudden change in direction of flow creating a hydrodynamic

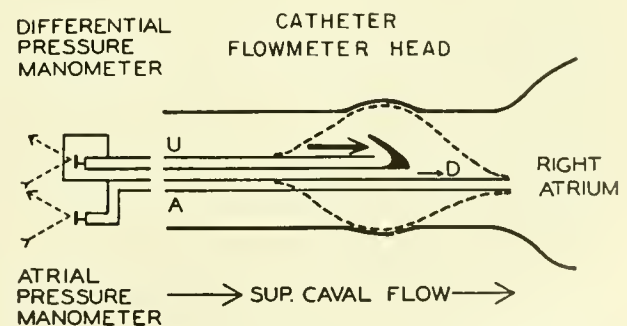


FIG. 13. Pitot "torpedo" of Brecher for recording superior vena cava flow. For description see text. [From Brecher (8).]

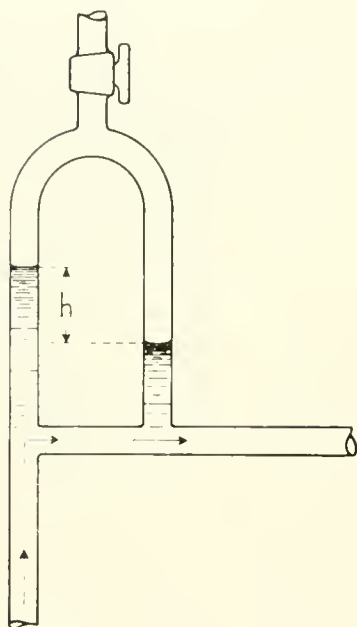


FIG. 14. Cybulski's modification of the Pitot meter. [From Müller (95).]

pressure elevation which acts upon the adjacent limb of the differential water manometer.

Broemser's differential sphygmograph (14) was built for application on unopened arteries. The instrument (fig. 15) consists of a double sphygmograph capsule, the two lower openings of which are covered with thin rubber diaphragms. The planes of the diaphragms form an obtuse angle to each other. The air-filled capsules are connected to an optical differential manometer as well as to a simple optical manometer. When the lower end of the instrument is pressed against an artery so that one diaphragm is directed upstream, the other downstream, a wedge-shaped inflection of the vessel wall is produced, and the blood pressure bulges the diaphragms into the capsules. Due to the pressure difference effected by the blood flow, the upstream diaphragm will bulge more than the downstream one; thus a flow-related deflection of the differential manometer takes place, while the deflection of the simple manometer is proportional to the blood pressure. The function of this device may be derived partly from the Venturi and partly from the Pitot principle in that the wall inflection is typical of the Venturi meters while the inclination of the diaphragms to the vessel axis results in a Pitot effect. The calibration curve determined by perfusion of excised arteries or of elastic tubes is almost quadratic. Although the records obtained with this device from the ascending and abdominal aorta of rabbit, cat, and

dog show the typical contours known from other flowmeter registrations, the instrument did not find frequent application. This may be due to the fact that its exact positioning and its calibration *in situ* are difficult.

Besides historical notes, Müller (95) published a theoretically and experimentally based criticism of Pitot meters. He stated that the arguments raised by previous investigators against these meters are, on the whole, not justified. Pieper & Vogel (101) calculated, for the device shown in figure 11, the distortions due to term III of equation 8 at various distances L . Although, on the one hand, L should be kept as small as possible so as to minimize C_3 , the flow sensitivity of the device (term II) is, on the other hand, also diminished when opening 2 is placed too near to 1. The optimal L must therefore be found by compromise. Hardung (57) came to the conclusion that, for instruments such as shown in figure 10, term III can theoretically be eliminated by placing the upstream-facing opening at a certain optimal distance from the long axis of the lateral tube.

A new and interesting catheter-tip method for recording the blood velocity in great central arteries was developed by Fry *et al.* (46-48). The tip of the double-lumen catheter used has two openings, both facing in lateral direction and placed several centimeters apart. Here the difference of the pressures acting on the openings ("axial pressure gradient") is due neither to a Venturi nor to a Pitot effect so that only the terms I and III of equation 8 are involved. While, in the aforementioned instruments, term III is a very undesired source of distortions, this very term plays the main role in Fry's method. For this reason, the coefficient C_3 is purposely made very large by choosing a great distance between the openings. It is obvious that the time course of the pressure difference itself, which is picked up by an electrical differential manom-

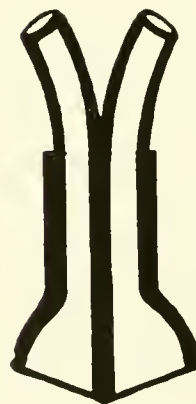


FIG. 15. Differential sphygmograph of Broemser for application to unopened arteries. Thin lines at the lower ends = rubber diaphragms. Upper ends connected to differential and adding manometers. [From Broemser (14).]

eter, in no way represents the time course of the flow velocity v . The magnitude v , however, is contained in the linear differential equation which remains when term II is removed from equation 8. In order to solve this equation for v continuously, the electrical signal delivered by the differential manometer is fed into an analogue computer which has been adjusted according to the magnitudes C_1 and C_3 . The output signal of the computer will then follow the actual flow course, provided the coefficients C_1 ("velocity resistance") and C_3 ("velocity inductance") are known with sufficient accuracy and the pressure difference is not affected by other physical influences. Difficulties arising from these conditions are discussed by Fry (46) and by McDonald (93). Flow records from the ascending aorta of dog and man demonstrate this method to be promising, while records of the pulmonary artery flow seem to require further clarification. For simplified catheter-tip approaches, consult the papers of Evans (29), Jones *et al.* (71), and their discussion by McDonald (93).

Many types of differential manometers have been used to record the pressure differences delivered by the instruments described above. It is obvious that low frequency manometers, particularly water manometers, are far from able to follow the rapid fluctuations in differential pressure which occur when arterial or central venous flow is recorded. Therefore membrane manometers with adequate frequency response are required for recording pulsatile flow. Their sensitivity must be considerably higher than that of common blood pressure recorders because the flow-related pressure differences are relatively small.

The difficulty of combining high sensitivity and high natural frequency in the same instrument is manifest in the discussions of physical principles by Frank and the models designed by Frank (37, 39), Gregg (54) and Green (50, 51).

The difficult task of recording the very small flow-conditioned pressure differences is made possible by the amplification of electrical signals from relatively stiff manometers of high natural frequency. Most important of these are capacitance or inductance manometers as well as resistance manometers of the strain gauge type (6, 50, 51).

It has been emphasized that, due to term II of equation 8, the calibration curve of most differential-pressure flowmeters is not linear. As in the case of bristle flowmeters, an attempt has been made to avoid the cumbersome graphical correction of records by using linearizing or, especially, square-root extracting devices, some of which *a*) are employed after registra-

tion, for evaluation of the records, while others *b*) are designed to deliver already linearized registrations. For *a*, Frank (39) proposed a photographic projection method; Broemser (15) and Ranke (108) combined the linearizing element with a planimeter. For *b*, Schroeder (119), as described above, uses optical linearization which works during the registration; Baxter & Pearce (4) connected a linearizing circuit to the electrical differential manometer. See also Green (50).

Finally, the so-called constant-pressure flowmeters or air-expansion systems may be mentioned although they are not differential-pressure meters in the proper sense [see Gregg (54), Green (50)]. If a blood reservoir is connected to a large air chamber, any inflow or outflow of blood will change the air pressure. The rate of volume flow of the blood entering or leaving the reservoir can therefore be determined from the slope of the change in air pressure which is recorded by a sensitive manometer. If the pressure variations are very small as compared to the absolute pressure level, the system delivers a virtually constant pressure for perfusing a vascular bed and acts, at the same time, as a flowmeter. Such systems have been preferentially employed for studies on the coronary circulation [Wiggers & Cotton (137); Green & Gregg (52); Eckstein *et al.* (25)].

THE ROTAMETER

The rotameter used in physiological experiments is a device for measuring mean blood flow in cannulated vessels. The prototype instrument was designed for measuring gas flow. In a vertical conic tube a float moves up and down in proportion to the rate of flow, stabilizing its position by fast rotation which results from spiral grooves around the float body. This rotation has given the instrument its name. If fluid instead of gas is used, the float does not rotate: stabilization is achieved by other means. Devices in use are based on designs by Gregg *et al.* (56). The instrument of Shipley & Wilson (121, 122) is shown in figure 16. The conic tube is made of Lucite or plexiglass with various flow capacities from 0.1 to 3.0 liters per min. The movement of the brass float is detected electromagnetically. An iron rod pierces the middle of the float vertically and is fixed in such a position that it protrudes equally above and below the body of the float. The lower part of the rod is guided by a ring, whereas the upper part enters into the lumen of an electromagnetic coil fed by alternating current. As the

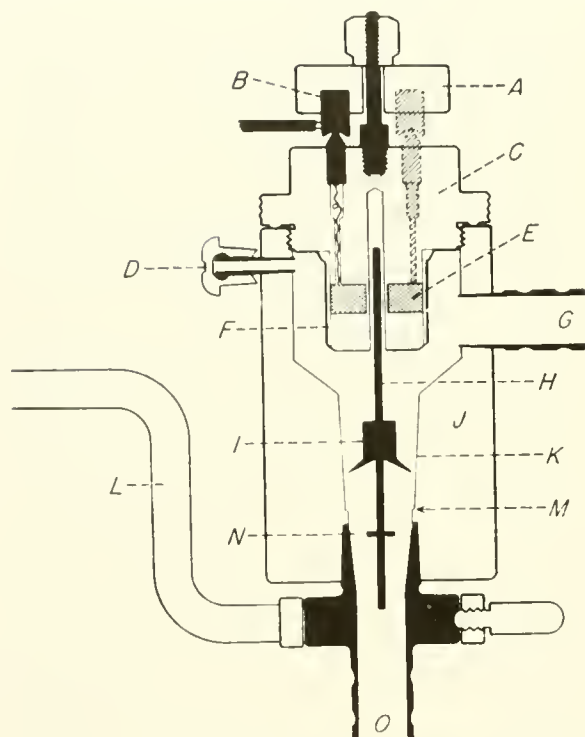


FIG. 16. Rotameter of Shipley and Wilson. *A*, contact holder; *B*, one of the contacts to induction and compensating coils; *C*, detecting assembly; *D*, rubber cap for removing air bubbles; *E*, coils; *F*, protecting sleeve; *G*, outflow spout; *H*, soft-iron float wire; *I*, brass float; *J*, metering chamber; *K*, conical metering portion; *L*, support; *M*, float rest at zero flow; *N*, float guide; *O*, inflow spout. [From Shipley & Wilson (121).]

rod moves into it, the inductance of the coil increases, and this is recorded continuously by means of a bridge circuit, rectifier, and galvanometer. Since the lift of the float is proportional to the flow of blood, the record can be calibrated in terms of flow rate.

The theoretical basis of the rotameter may chiefly be derived from mass inertia of the streaming fluid according to the Bernoulli effect. The fluid streaming upward is accelerated in the ring slot around the float. The fluid reaches its maximal velocity not in the plane of the slot, but at a somewhat higher level. This velocity difference causes a pressure difference to develop between the levels below and above the float. Other effects, such as eddy formation, may play an additional role. The pressure difference is augmented by friction due to viscosity of the fluid. By the action of the total pressure difference on the cross-sectional area of the float, a force is brought about which lifts the float, a force is brought about which lifts the float. In steady states the lifting force must be in balance with the float's weight diminished by its buoyancy.

Since the weight minus buoyancy remains constant, the force must be constant also. This is achieved by the fact that the ring slot area increases with flow rate by elevation of the float to a higher level where the tube diameter is larger.

Since the rotameter should be independent of viscosity (due to changes in temperature or hematocrit), the frictional force must be kept minimal as compared to the inertia force. This can be achieved either by increasing the inertia force by special shaping of the float (121) or by diminishing the frictional force by using large ring slot areas and floats of light weight (60).

The relationship of volume flow to galvanometer deflection can be made linear if the electrical settings are adjusted. Since the response to changes of flow is slow, only mean flows are recorded. However, large pulsations, such as occur in arteries, are not averaged correctly, particularly by units which use heavy brass floats. This results in the recording of lower mean values than are actually present (60), and it may be useful in such cases to diminish the amplitudes of the flow pulsations by an air chamber arranged upstream from the rotameter (122).

THE ELECTROTURBINOMETER

The Potter electroturbinometer, originally built for technical purposes, has been applied by Sarnoff *et al.* (116, 117) for the registration of aortic blood flow in dogs. It consists of a stainless-steel turbine which is driven by the blood stream. The turbine is suspended within a Lucite tube by spring clips. The necessity of using thrust bearings is avoided by shaping the rotor in such a way that the stream generates, in addition to rotation, a hydrodynamic force which acts in an upstream direction. The rotor contains a permanent magnet which induces, by its rotation, an alternating voltage in a pickup coil outside the tube. The frequency of that voltage is proportional to the rotational speed; by means of a counting and integrating electronic system, an output signal is obtained, the strength of which is a measure of the number of turbine revolutions per time unit. Two models of different sizes are described, the smaller of which responds to flow from about 0.5 to more than 4.5 liters per min. The calibration curve shows a slight bend and is, in the case of blood, independent of temperature from 22 C to 40 C and of the hematocrit down to 22 per cent. Although the instrument is unable to follow the instantaneous changes of the aortic

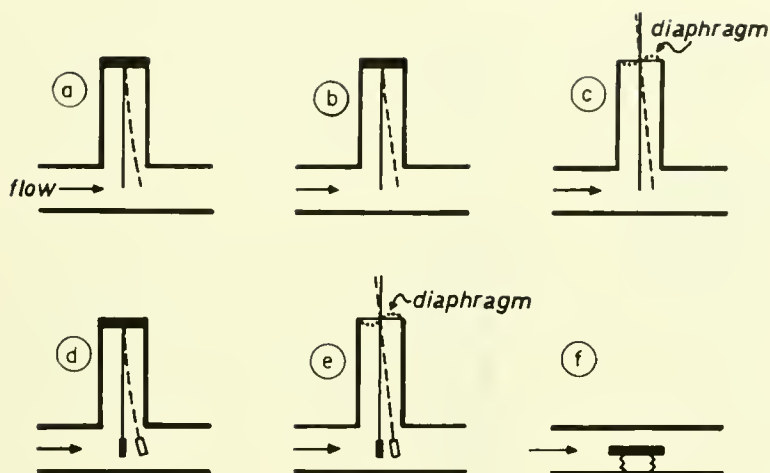


FIG. 17. Schematic diagram of different arrangements of bristle and pendulum flowmeters. *a*: Bristle in the proper sense. *b*: Stiff needle with flexible origin (short flat spring or similar). *c*: Stiff needle the fulcrum of which is formed by a diaphragm. *d*: Similar to *a* or *b*, with a body at the tip. *e*: Similar to *c*, with a body at the tip. *f*: Coaxial compact cylinder, held by one or two springs. The types *a*, *b*, *c* are now commonly called "bristles," the types *d*, *e*, *f*: "pendulums." [Redrawn and modified from Taylor (127).]

flow pulses, it is said to indicate mean flow faithfully, irrespective of whether the flow is steady or pulsatile, provided no phases of essential backflow occur. Its resistance to blood flow is relatively high. The small model causes pressure drops of about 5, 13, 30, and 50 mm Hg at flow rates of 1, 2, 3, and 4 liters per min, respectively. The pressure drops caused by the large model are lower. Heparinization of the dogs is, of course, necessary. Some alteration of the pulse wave and hemolysis might be caused by the instrument.

BRISTLE AND PENDULUM FLOWMETERS

When a body is immersed in a streaming fluid, it represents an obstacle to the flow. The force exerted on the body by the streaming fluid is due partly to friction and partly to mass inertia of the fluid. According to Frank (40), this force F is given approximately by the formula:

$$F = C_1 v + C_2 v^2 \quad (10)$$

where v = velocity of the fluid acting on the body; C_1 and C_2 = coefficients which depend on the viscosity and density, respectively, of the fluid, on the size and shape of the body, and on the local distribution of velocities; $C_1 v$ = frictional term; $C_2 v^2$ = inertia term. Sometimes, another approximation is used:

$$F = C v^k \quad (11)$$

where, in case of blood, the exponent k is found to be between 1.2 and 2.0. As will be discussed below, theoretical estimation of the coefficients and of the exponent is impossible except under very simple conditions,

so that an empirical determination is usually necessary.

If the body is held in its position by an elastic device, it will undergo some displacement due to the force F , and thus the degree of displacement can be taken as a measure of that force. Since the force is related to the fluid velocity, according to equation 10 or 11, the registration of the displacements by mechanical, optical, electrical, or other means represents a continuous recording of the flow. For the construction of such devices, the following requirements should be taken into account: *a*) The resistance to flow produced by the obstacle must be so small that the flow is not significantly influenced. *b*) Where pulsatile flow is to be recorded, the natural frequency of the elastically suspended body must be much greater than the highest significant frequency. If this condition is fulfilled, the displacements of the body will be very small. *c*) As far as possible a fixed relationship should be obtained between force and displacement on the one hand and average flow velocity on the other, independently of the velocity profile. This will be discussed below.

The body itself can be in the form of a rod or needle set perpendicularly to the direction of flow. This needle is usually attached at its origin to the end of a side tube while its tip remains free and reaches the axis of the main tube as shown in figure 17*a* to *c*. In some devices, the needle is longer. If the origin is totally fixed whereas the needle itself is flexible, it will be called a bristle in the proper sense (fig. 17*a*). In most cases the needle is rigid, but is allowed to move about a fulcrum (fig. 17*b* and *c*). While this type physically represents a pendulum, it is now usually called a bristle, too. The common characteristic

of these types is that they are placed radially so that all fluid particles moving across a radius between the axis and the wall will participate in causing the needle's deflection.

In the "pendulum" type of figure 17*d* to *f*, however, the device is represented either by an elastically suspended coaxial cylinder (fig. 17*f*) or by a needle which carries at its tip a body with a resistance to the flow that is very great as compared to that of the needle (fig. 17*d* and *e*). In these cases, the deflections are caused mainly by the axial flow. This renders greater sensitivity than a simple needle, but interferes with the flow to a higher degree and increases the errors which result from changes of the velocity profile.

The first model of a hydrometric pendulum was employed by Castelli [1577-1644, quoted from (96)]. It consisted of a sphere which was suspended on a thread and submerged in the streaming water. The angular deflection of the thread from the vertical was used as a measure of the flow velocity. In this author's honor, Müller (96) proposed that the principle of all similar flowmeters be called the "Castelli principle." On an analogous theoretical basis, Michelotti (1710-1777) built a hydraulic balance (96).

Vierordt [1858, quoted from (38)] was the first to apply the hydrometric pendulum to the measurement of blood velocity, but his instrument was far from perfect.

The hemodromograph of Chauveau and Lortet [1860 and 1867, quoted from (38)] was the first model of a hydrometric pendulum which allowed continuous recording of the blood velocity. The design was similar to that of figure 17*e*. A rubber diaphragm represented the fulcrum beyond which the lever of the pendulum was prolonged so as to act on an air-transmission system. Noteworthy progress was achieved by this device although the natural frequency was not high enough and blood pressure variations changed the position of the rubber diaphragm which held the pendulum.

Frank (40) presented some basic theoretical principles of the hydrometric pendulum and of the mechanical conditions necessary for adequate frequency response. He also stated that submerging the pendulum into fluid markedly increased the damping of free vibrations while only slightly lowering the natural frequency. From this he concluded that the mass of fluid adhering to the pendulum must be relatively small. He built an elastically suspended pendulum for optical registration (40).

The first attempt at transmitting the pendulum deflections electrically was made by de Burgh Daly

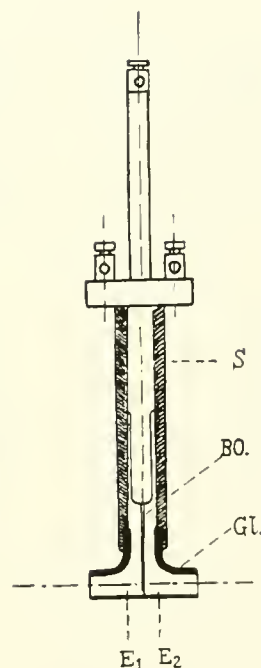


FIG. 18. Bristle flowmeter of Holzlöhner and Bergmann. GL, glass cannula; BO, bristle; E_1 and E_2 , platinum electrodes; S, vertical tube. [From Bergmann (5).]

(21), who installed, in the vertical limb of a T-cannula, a condenser composed of two copper foils, one being attached to the pendulum rod and the other being placed on the outside surface of the side tube. The variations of capacity of this condenser were caused by the pendulum deflections and detected by high frequency and rectifier circuits.

Another type of electric transmission was applied by Holzlöhner (61), who used the streaming blood itself as an electrical conductor. In his device, three electrodes are placed in the flow cannula (fig. 18) so that they form two limbs of a Wheatstone bridge. The bristle, belonging to the type of figure 17*a*, represents the middle electrode and consists of a thin platinum wire covered by a fine glass coating. At the bristle tip, the wire is bare and in direct contact with the blood. Two other platinum electrodes are placed in the tube wall upstream and downstream at equal distances from the bristle tip. When the bristle is bent by the blood stream, the ratio of the resistances on both sides of the bristle tip is changed. The electric equipment contains the resistors completing the bridge circuit, a 20-kc per sec oscillator, an a-c amplifier, and a rectifier. Holzlöhner called his instrument "Strom-(borste)." By translating this name into English (Borste = bristle), Brecher (12) introduced the expression "bristle flowmeter" into the literature, where it is now commonly used in connection with all types shown in figure 17*a* to *c*. Holzlöhner's model was modified by Bergmann (5) and employed for recording flow in the

carotid artery and in the jugular vein (62). Its sensitivity and frequency response were satisfactory. However, the base line was often shifted by spontaneous changes of the resistances between the electrodes. This was probably due to minute fibrin deposits at the bristle tip (102).

Further improvement of the electrical transmission was achieved with electromagnetic devices. The bristle or pendulum is made of or mounted with ferromagnetic material which changes, by variation of its position, the magnetic field of two coils installed on both sides of the pendulum. The coils are fed with alternating current. In 1952, Brecher and Crun [quoted from (9)] arranged two induction coils around a Lucite cannula in such a way that deflections of ferromagnetic pendulum changed the coil inductances in opposite directions. Although the signal-to-noise ratio was high, temperature changes produced an unfortunate instability of the base line.

Pieper & Wetterer (102-104) developed several models with electrical transmission based on the principle of the differential transformer. While in the inductance bridge the amplitude of the resulting signal voltage is the outcome not only of changes in inductance, but also of changes in ohmic resistance, e.g., resulting from temperature changes of the coil wires, the differential transformer separates the ohmic component from the inductive component so that only the latter is measured. The transformer consists of two symmetrical parts, each of which contains a primary and a secondary coil. The primary coils, which are fed with alternating current of 5 to 10 kc per sec, are connected in series so that the directions of their magnetic a-c fields are congruent. The secondary coils are also arranged in series; their winding directions, however, are opposite to each other, and the induced secondary a-c voltage will be proportional to the difference of the mutual inductances present in each of the two parts of the transformer. When the conditions are equal on both sides, the secondary voltage will be null. By shifting the ferromagnetic core, the mutual inductance of one part is augmented, and that of the other part diminished. If the primary alternating current is kept constant, changes in ohmic resistance of both the primary and secondary circuits will have no influence on the secondary voltage. This principle had already proved satisfactory in micromanometers (49, 135). The first pendulum flowmeter of Pieper and Wetterer consisted of a compact ferromagnetic cylinder (fig. 17*f*) the deflections of which were detected by differential-transformer coils wound around the tube upstream and downstream from the

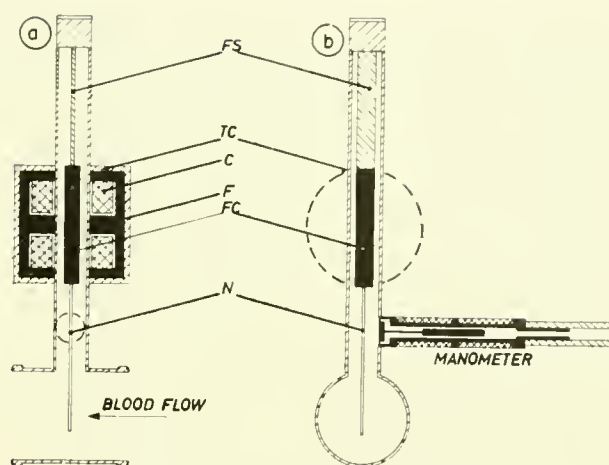


FIG. 19. Electromagnetic bristle flowmeter of Pieper and Wetterer. *a*: Section in the plane of the two axes of the T-cannula. *b*: Section at 90° to *a*. FS, flat spring; TC, transformer case; C, coils of differential transformer; F, ferromagnetic frame of transformer; FC, movable ferromagnetic core; N, needle. Proportions not to scale. Maximal length of side branch about 20 mm. For use, the T-cannula is completely filled with anticoagulant fluid. [From Pieper & Wetterer (104).]

middle of the cylinder. This model was abandoned in spite of its simplicity because of two disadvantages: The cylinder length is not negligible so that the inertia of the fluid column around the cylinder gives rise to a third term in equation 10 which is proportional to the flow acceleration and may distort the records (see term III in equation 8). In addition, the force exerted on the cylinder by the streaming fluid is due only to the flow near the axis.

The authors, therefore, built two other models, the second of which corresponds to figure 17*b* and is shown in figure 19. A flat spring is fixed at the end of the vertical limb of the T-cannula and carries a ferromagnetic core and a needle protruding into the horizontal tube. The differential transformer is installed on both sides of the vertical limb so that deflections of the needle will shift the core toward one or the other transformer part. The device has a high sensitivity and satisfactory temperature stability. Its natural frequency is about 200 cps. The additional equipment consists of an a-c source of 5 to 10 kc per sec for feeding the primary coils of an amplifier and a rectifier. Attempts to linearize the calibration curve have also been made. A micromanometer was attached to the T-cannula (fig. 19) for simultaneous blood-pressure recording. The instrument was used for the registration of pressure and flow in the carotid and femoral arteries of dogs.

Independently, Scher *et al.* (118) described a paddle

flowmeter, the deflections of which are detected either by two coils acting as two arms of an inductance bridge or by four coils forming a differential transformer. The coils are wound around the flow cannula upstream and downstream from the pendulum. This pendulum consists of a flexible ferromagnetic paddle or of a spring-suspended ferromagnetic disk fixed on the inner side of the tube wall. The authors emphasized improvement in stability achieved by using the differential transformer. They implanted such devices into the abdominal aorta of dogs under anesthesia and obtained flow records some days later, the animals being conscious.

The most recent model of a pendulum flowmeter with electromagnetic transmission was built by Pieper (100). The flow-sensing element containing a differential transformer is arranged at the tip of a catheter and can be introduced from a peripheral vessel into an unopened central vessel, e.g., from the carotid into the ascending aorta. The transformer coils are wound around a longitudinal iron core. A ferromagnetic cylinder, surrounding the coils at a small distance and covering about three fourths of their length, is suspended by elastic springs so that it can be shifted to and fro in its longitudinal direction. On its circumference, the cylinder carries a small ring-shaped disk which faces the blood stream. The force exerted on the disk by the flow will shift the cylinder and thus change the mutual inductances of the two transformer parts in opposite directions. The natural frequency of the elastically suspended cylinder is 120 cps per sec. The frequency response was found to be flat up to 20 cps. The probe is held centered in the vessel axis by an umbrella-like arrangement. Rods surrounding the probe are folded when the catheter is introduced, and are spread by means of a mechanism actuated from outside when the tip has reached its final position.

The RCA 5734 transducer tube represents a new and very useful means of electrical transmission in pendulum and bristle flowmeters. This tube, which was originally built for physical purposes, was employed in physiology for the measurement of small forces, such as in the manometers and sphygmographs. The essential characteristic of the 5734 triode is the movable element consisting of the internal tube plate (anode) and the external plate shaft (fig. 20). This movable element extends through a thin and flexible metal diaphragm, the center of which acts as a pivot permitting small angular deflections of the plate shaft so that the distance between the plate and the fixed grid will be changed. This results in changes of the plate current. Under the triode-operating condi-

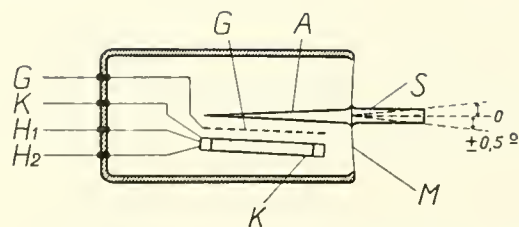


FIG. 20. Mechano-electric transducer tube no. 5734 of the Radio Corporation of America. Schematic sectional view. [Redrawn from Müller (96).] *K*, cathode; *H*₁, *H*₂, heater (filament) connections; *G*, grid; *A*, internal plate (anode); *S*, external plate shaft; *M*, flexible metal diaphragm. *A*, *M*, and *S* are electrically connected to the tube's metal shell. Terminal leads in clockwise order. *Bottom view*: heater, grid, heater, cathode. Tube dimensions as indicated by RCA: maximal total length (excluding leads), 1.3". Maximal diameter, 0.328". Tube weight, 1.75 g. Rotational compliance of the diaphragm, 0.075 degree/g cm. Resonance frequency of plate shaft, 12,000 cps. The connection of the plate to the electric circuit is provided by the supporting clamp attached to the metal shell of the tube. If there exists contact between tube shell and blood or tissues, the electric circuit has to be designed in such a way that the tube plate is grounded. The plane of deflection of the plate shaft must coincide with the plane through terminal lead of grid and tube axis.

tions indicated by RCA (plate-supply voltage, 300 volts; grid voltage, 0 volts; load resistance, 75,000 ohms), the deflection sensitivity, i.e., the ratio of change in output voltage to angular deflection of the plate shaft, amounts to 40 volts per degree. Deflections of more than ± 0.5 degree from the normal position of the shaft may damage the diaphragm and the tube electrodes. By virtue of its small weight and dimensions, its high sensitivity and the low inertia of its moving part, the 5734 is very appropriate to use in constructing a pendulum or bristle flowmeter. A further advantage is its commercial availability.

In 1953, the 5734 was first used for blood flow measurement independently by Brecher and his co-workers, and by Scher *et al.*, and in 1954 by Müller. Fundamentally, all these designs were based on the principles shown in figure 17*c* and *e*. The transducer tube is placed in the side branch of a T-cannula, and a needle or pendulum which protrudes into the streaming blood is attached to the plate shaft.

In the model of Scher *et al.* (118), the T-cannula is made of stainless steel. Two types of obstacle to flow are used, the first being a flat paddle placed across the stream, the second a streamlined rod or tube of plastic. As can be expected, the sensitivity of the paddle type is very high, and the deflection is approximately proportional to the square of flow velocity so that in such cases the second term of

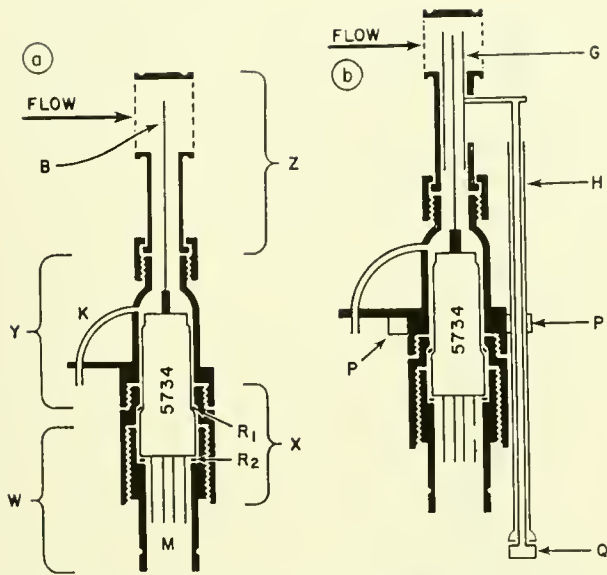


FIG. 21. Diagram of the standard transducer-tube bristle flowmeter of Brecher. *a*: Flowmeter cannula similar to that of Brecher & Praglin (12), with improved socket. *b*: The same model with "zeroing" cylinder. Total length, 50 mm. For further description see text. [From Brecher (9, 10).]

equation 10 is preponderant. The streamlined obstacle, however, offers much lower resistance to the flow; its sensitivity is therefore smaller, and its calibration curve approaches linearity in that the deflection is proportional to $v^{1.2}$, thus indicating that it is chiefly due to viscous drag. It may be noteworthy that the authors found the output voltage of the transducer tube to respond to cooling by the streaming blood so that the base line of the records was not sufficiently stable.

The most extended use of the 5734 tube-bristle flowmeter in arteries and veins was made by Brecher *et al.* Their "standard model" was published by Brecher & Praglin (12) and is shown in figure 21 with two additional improvements described by Brecher (10). The system consists of four parts *X*, *Y*, *W*, *Z*, which are screwed together. The transducer tube is held by the parts *X* and *W* which form a metal screw socket pressing the two lead washers *R*₁ and *R*₂ against the lower rim and shoulder of the tube's metal shell. In this way, the tube is fixed, and permanent electrical contact is established between tube plate and grounded cannula. Also seepage of fluid from part *Z* to the lead wires *M* is prevented. Part *Z*, as "head" of the assembly, is ligated into the blood vessel and connected with *X* by part *Y*. Heads of various dimensions are available for use in blood vessels of different diameters. The small bristle *B* is

20 to 35 mm long; it can be made of glass, nylon, or metal. The natural frequency of the transducer system with the bristle amounts to about 200 cps. The side tube *K* is used for the removal of air bubbles and for attaching a manometer for pressure recording. Temperature changes of the transducer tube caused by the streaming blood are prevented by the long stationary fluid column in the parts *Y* and *Z*. When the meter is inserted into the blood vessel, zero flow can be determined at any time by means of the "zeroing" cylinder *G* (fig. 21*b*) without stopping the blood flow. The cylinder position is controlled by the handle *Q*; it can be moved forward beyond the bristle tip in order to protect the bristle from deflection by the flow.

For blood-flow recordings in large arteries, especially in the trunk of the pulmonary artery, Brecher & Hubay (11) developed a modification of the standard bristle flowmeter which can be inserted without clamping the vessel (fig. 22). The device consists of three main parts *A*, *B*, *C*. The transducer tube is fixed in *C* by cement. The most characteristic part of the device is the lip *D* which is introduced into the vessel through a "buttonhole" opening with little loss of blood. The vessel wall is then firmly held between *D* and plate *E*, the latter being pressed by screw nut *F*. In order to protect the bristle against damage during the insertion of lip *D* into the vessel, the tip of the bristle *U* is withdrawn behind lip *D* by screwing part *C* backward. The

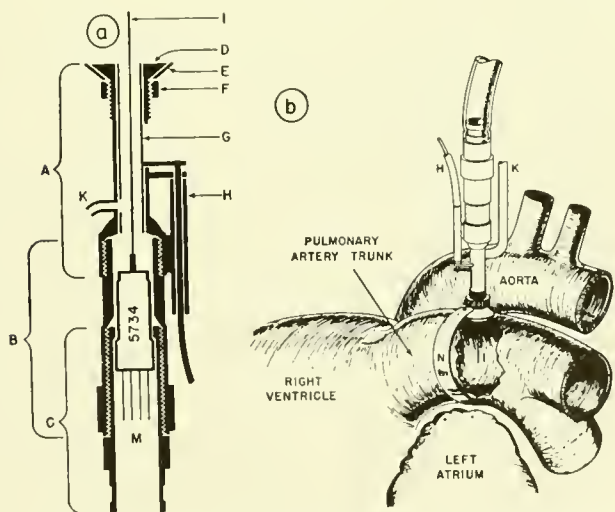


FIG. 22. Brecher's bristle flowmeter modified by Brecher & Hubay (11) for use in large arteries, especially in pulmonary artery trunk. Total length, 75 mm. *a*: Diagram of longitudinal section. *b*: Application to pulmonary artery. For description see text. [From Brecher (10).]

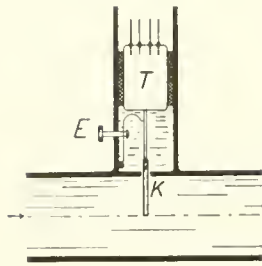


FIG. 23. Schematic diagram of the transducer-tube flowmeter of Müller. *T*, 5734; *E*, micrometer screw. *K*, resistance body. [From Müller (96).]

artery's diameter is kept constant by the metal band *N* placed around the vessel wall. As in the standard model, the "zeroing" cylinder *G* is used for the determination of the base line of flow during the records, and the side tube *K* for the removal of air bubbles and for manometer connection.

As to the additional electrical equipment, Brecher uses a load resistor of 500,000 ohms for the transducer tube which gives higher sensitivity and better d-c stability than the 75,000-ohm resistor recommended by RCA. The load resistor is connected to the cathode while the plate is grounded in all cases. The changes in plate current due to the deflections of the plate shaft cause proportional variations of the cathode potential which are amplified either by battery-operated or main-fed d-c amplifiers. Both types were designed by Praglin and are described by Brecher (9). It should be noted that the greatest plate-shaft deflection ever observed in Brecher's blood-flow experiments is 3 min of arc. This deflection results in a potential change of 4 volts at the tube's cathode, corresponding to a sensitivity of 80 volts per degree. Thus the deflections caused by the blood flow remain within the mechanically safe range, which extends to 30 min of arc on either side.

The transducer-tube flowmeter developed by Müller (96) is shown in figure 23. It was built for flow measurement in blood vessels as well as for investigations of more general hydrodynamic interest, particularly for the study of the forces exerted by streaming fluids of various Reynolds numbers on resistance bodies of different shapes. An accurate calibration in terms of force is therefore needed and can be performed by the micrometer screw *E* which causes a small spring to press on the tube's plate shaft. The transducer tube is arranged in a bridge circuit, the adjacent limb of which contains a second triode of similar properties which compensates for fluctuations of operating voltage, etc. The bridge output is connected to a push-pull d-c amplifier. A special model for coronary-artery flow recording was designed by Laszt & Müller (86) (fig. 24). The hori-

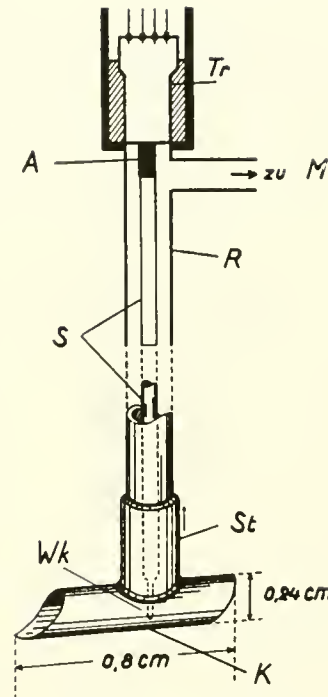


FIG. 24. Transducer-tube flowmeter of Laszt and Müller. *T_r*, 5734; *A*, plate shaft; *M*, manometer; *R*, vertical limb of T-cannula; *S*, extension rod of bristle. *St*, movable cylinder around *R*; *Wk*, cylindrical resistance body at the bristle tip; *K*, horizontal limb of T-cannula. [From Laszt & Müller (86).]

zontal cannula *K* is inserted into the vessel without interruption of the flow and without using ligatures around the vessel. The vessel wall is pierced by the sharp edge, and the cannula is tilted and moved slightly until *K* slips into the vessel. The cylinder *St* is then pressed downward to immobilize the vessel wall around the incision.

Critical remarks on the bristle flowmeter technique are based on experimental data and on theoretical considerations. The main practical advantages enumerated by Brecher (9) are as follows: negligible resistance to and interference with the flow; equal and opposite response to forward and backward flow; high sensitivity and frequency response. The main practical disadvantages are: necessity for opening the vessel and using anticoagulants; gravitational effects on the bristle when the position of the cannula is altered; and the nonlinearity of the calibration curve. This latter drawback can be overcome by electrical linearization (9, 103). Since, for this purpose, the amplification of low flow signals is made much greater than that of high ones, the device becomes very sensitive to minute shifts of the base line so that an exceedingly stable base line is required. The

linearizing circuit has to be adjustable to correct the calibration curves in the range from about $v^{1.2}$ to $v^{2.0}$. In case of large flow pulsations, the recording of the mean flow by integrating circuits must be preceded by linearization. Obviously, some of these properties concern other flowmeters as well (particularly differential-pressure flowmeters). As to flowmeters which are equipped with the transducer tube, the temperature of material surrounding the tube should be kept constant, and the heater current should be stabilized. Furthermore, some 5734 tubes show "pressure artifacts," i.e., changes in plate current when the pressure exerted on the tube's diaphragm is altered. According to Brecher, very few new factory-delivered tubes respond to pressure; however, careless handling of a tube, especially anything causing deflections of the plate shaft beyond 30 min of arc, can effect permanent distortion of the diaphragm which will give rise to such artifacts.

Müller (96) showed theoretically that at present, exact mathematical calculation of the forces exerted on a body immersed in the streaming fluid is impossible even in the case of steady flow. Only in the range of very small Reynolds numbers will forces be fully calculable as the sum of a term proportional to v and another term proportional to v^2 (cf equation 10). Also, in the range of high Reynolds numbers, friction cannot be ignored. For the force exerted on the body is due to a thin boundary layer of fluid around its surface (Prandtl's theory). Within this layer, the velocity gradient perpendicular to the body surface is very high. The lower the fluid's velocity, the thinner will be the boundary layer and the greater the velocity gradient. Müller's experimental data show that the boundary layer around a streamlined bristle is stable up to Reynolds numbers of about 900; above this, disturbances of the layer and hence irregularities of the force exerted on the bristle are observed, even if the flow is laminar. As to pulsatile flow in blood vessels, the conditions are still more complicated as the blood is nonhomogeneous and a very large range of Reynolds numbers (from 0 up to several thousand) may occur within one pulse cycle. According to Müller's experimental findings as well as to Womersley's theory, the fluid laminae moving at various distances from the vessel axis are oscillating out of phase with each other. Thus, one must consent to Müller's conclusion that, from a theoretical point of view, this type of flowmeter type is far from having a clear theoretical and mathematical basis.

Taylor (127) simplified some of the physical presumptions and presented a valuable theoretical

study of the recording properties of bristle and pendulum flowmeters. Considering the velocity profile at various frequencies (fundamental and higher Fourier harmonics) of oscillatory flow according to Womersley's theory, he found that simple bristles (see fig. 17*a*, *b* and *c*) give relatively true records of the oscillatory flow. Compared with their response to steady laminar flow, these instruments progressively underestimate the average velocity as the flow oscillations increase in frequency. The error in amplitude approaches 25 per cent at higher frequencies, and the maximum phase lag is about 7°. Taylor also compared an actual femoral-artery flow curve [recorded by McDonald (92) with gas-bubble high-speed cinematography] to the record which a bristle would give according to his calculation. He showed that the errors which are mainly due to the higher harmonic components have no great distorting effect because of their small amplitude. In Taylor's words, "the final 'recording' is a quite acceptable reproduction of the flow." Attaching a paddle to the bristle (fig. 17*d* and *e*) gives rise to greater errors in amplitude and phase while the recording by a coaxial cylinder (fig. 17*f*) shows small errors in amplitude, but an enormous phase lead at higher frequencies. In case of an almost flat velocity profile, as in the great arteries near the heart, bristles and even paddle-mounted pendulums will give still more satisfactory results.

METHODS BASED ON THE ELECTROMAGNETIC-INDUCTION PRINCIPLE

This type of flow measurement is notable in several respects. It furnishes direct transformation of the mechanical magnitude into an electrical signal. Its interference with the blood flow is so small that it can be completely neglected. It delivers strictly linear calibration curves and equal sensitivities with opposite signal directions to forward and backward flow so that the assessment of mean flow by integrating circuits can be easily achieved. Its calibration in terms of average velocity or flow rate is independent of the velocity profile and of the density, viscosity, and temperature of the fluid. Its range of frequency response is theoretically unlimited and depends in practice on the electrical equipment used. It is applicable to all fluids having electrical conductivity equal to or higher than that of tap water, e.g., saline solutions, blood, mercury.

In addition to these physically inherent character-

istics which render the method almost ideal, there are other favorable properties of great practical value. Most important, the method is applicable to unopened blood vessels and therefore requires neither damaging the vessel wall nor using anticoagulants. For this reason, the method can be applied to the anesthetized animal and man under surgery and by implanting electromagnetic probes, measurements can be made on conscious and freely moving animals.

The electrical flow signal is produced by the motion of the fluid across the lines of a magnetic field. For explanation, a simple physical experiment is shown in figure 25. A metal strip is moving at a velocity v in the direction indicated by the arrows. This direction is at right angles to the lines of magnetic force present between the magnet poles N and S so that a voltage (potential difference) is generated in the metal strip according to Faraday's induction law. The induced voltage, which is directed perpendicularly to the lines of magnetic force and to v , is picked up by sliding contacts ("electrodes") e_1 and e_2 , and measured by the voltmeter V . Assuming that the magnetic field permeating the metal strip between the electrodes is homogeneous and that the lines of force, the velocity v , and the line extended between the electrodes are directed mutually at right angles to each other, the induced voltage E_{ind} is:

$$E_{ind} = BDv \cdot 10^{-8} \text{ volts} \quad (12)$$

where B = density of magnetic flux (gauss); D = width of the metal strip, which is also the distance between the electrodes (cm); v = instantaneous velocity of the metal strip (cm/sec). Reversal either of the direction of the magnetic field or of the motion will reverse the polarity of the induced voltage. Small deviations from the assumed right-angle arrangement between the directions of B and v , say by ± 10 per cent, have little effect on E_{ind} .

Now suppose that the moving metal strip in figure 25 is replaced by a conductive fluid streaming through a tube (fig. 26). The tube wall may consist of insulating material, and the electrodes e_1 and e_2 which are inserted into the wall may be in contact with the fluid. In this case, also, equation 12 is generally valid if D is the diameter of the fluid column and v the instantaneous fluid velocity. The velocity, however, will usually not be uniform within the space between the electrodes (as is the case for the solid strip of fig. 25). The induced voltage must therefore be calculated from the total sum of all differentials $v \cdot dr$

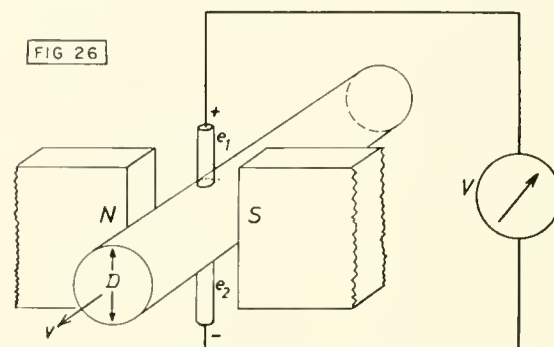
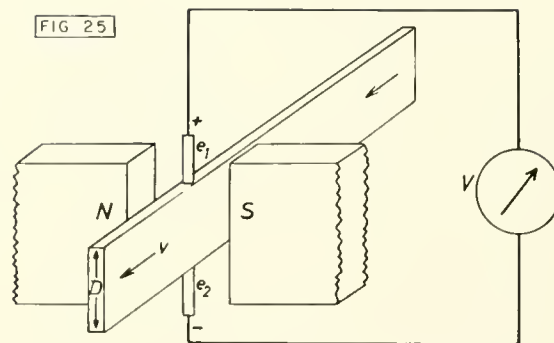


FIG. 25. So-called unipolar induction in a metal strip moving across the lines of magnetic force. For explanation see text.

FIG. 26. Basic arrangement for electromagnetic flow measurement. Metal strip of fig. 25 is replaced by conductive fluid streaming through a tube. For explanation see text.

existing along D , i.e., from

$$\int_{-R}^{+R} v \cdot dr = D \bar{v} \quad (12a)$$

where \bar{v}_R = velocity averaged over the diameter D or radius R . Thus, this velocity has to be used in equation 12 instead of v , and the induced voltage is obviously dependent on the velocity profile. This would be an essential drawback of the method, if there were not an additional compensating effect which is of the greatest importance. Let us assume that, as in case of steady laminar flow, the fluid near the axis runs much faster than that near the wall. The outer fluid layers, in which smaller voltages per unit length are induced than in the inner layers, act as a sort of load resistor to the latter, and circular electric currents take place within the fluid thus bringing about a change in the originally induced voltage distribution. Making a valuable theoretical and experimental contribution to the achievements of earlier workers (see historical notes), Thürlemann

(128) found that, due to this effect, the resulting voltage picked up by the electrodes is, in case of a parabolic velocity profile, just as high as E_{ind} would be if all the fluid layers were to move uniformly at the velocity \bar{v}_A averaged over the cross-sectional area. This means that the method delivers a flow-signal voltage which is linearly proportional to the instantaneous velocity \bar{v}_A or to the instantaneous flow rate. The only conditions required are that the magnetic field be homogeneous, that the fluid be homogeneous with respect to its electrical conductivity, and that the velocity distribution be symmetrical in relation to the tube axis (79). It follows that the flow-signal voltage E_f which is picked up by the electrodes differs from the originally induced voltage E_{ind} (except the extreme case of a completely flat velocity profile where both are equal) so that for fluid flow, equation 12, has to be modified to:

$$E_f = BD\bar{v}_A \cdot 10^{-9} \text{ volts.} \quad (13)$$

As Kolin (78-80) stated, equation 13 is valid also in case of any other velocity profile and even in the idealized case of a central and coaxial fluid jet which is moving through a tube while the annular fluid cylinder around this jet is quiescent. From this Kolin concluded that the electrically conducting vessel wall may be regarded as representing such a quiescent fluid cylinder surrounding the streaming blood and that, therefore, no error is caused if the voltage E_f is picked up by electrodes placed at the outer surface of the vessel wall. Thus the application of the method on unopened blood vessels, which had been carried out earlier as an experimentally proved procedure by Kolin and other workers, was also justified on a theoretical basis. Any inaccuracy due to the difference in specific conductivities of blood and wall tissue is of minor significance (80, 82).

If, instead of \bar{v}_A , the instantaneous flow rate \dot{Q} (cm^3/sec) is used in equation 13, we get with $D = 2R$ and $\bar{v}_A = \dot{Q}/(R^2\pi)$:

$$E_f = \frac{2B\dot{Q}}{R\pi} \cdot 10^{-9} \text{ volts} \quad (14)$$

It is obvious that, according to the aforementioned considerations, R is the vessel radius including the wall thickness. Equation 14 shows that the sensitivity E_f/\dot{Q} is inversely proportional to R or to the distance between the electrode tips and is independent of the wall thickness (80, 82), provided that B is fixed and that the vessel is surrounded by insulating material.

The history of electromagnetic flow measurement [see notes in (78, 84, 123)] shows that several authors found the principle independently of each other. Faraday demonstrated electromagnetic induction in solid as well as in liquid conductors. But he did not conceive the idea of measuring fluid flow which involves recognition of velocity distribution. His experiment at the Waterloo Bridge, in which he tried to detect an induced electromotive force (emf) in the River Thames due to the water's motion through the earth's magnetic field, simply represented his search for an induction phenomenon on a terrestrial scale. This experiment was unsuccessful, probably due to electrode-polarization difficulties. Young *et al.*, in 1920, were able to record such an emf. Williams, in 1930, performed the first electromagnetic measurements of the velocity distribution in copper sulfate solutions, but made no measurement of flow rate. In 1932, Fabre (30) suggested, in a short note, electromagnetic recording of variations in blood flow in cannulated vessels [see also (84)]. Kolin [1936 (5)] is to be regarded as the real founder of electromagnetic blood-flow measurement. He was the first to recognize the applicability of the method to unopened vessels and to obtain successful records from dogs. In the following years and decades, he also made the major contributions to further development of the procedure, especially by introducing and refining the a-c modification instead of the d-c type which was employed earlier. The d-c method was also described by Wetterer [1937 (133)] and was particularly used for recording flow in the unopened ascending aorta. Valuable contributions were further made by Einhorn (28) concerning the a-c method and by Thürlemann (128) whose findings have already been mentioned. In 1953, the square-wave modification was initiated by Denison (see 125) and, since then, has been undergoing considerable development by the work of Denison and Spencer. It combines, at least theoretically, the advantages of the d-c type with those of the a-c sine-wave type.

The d-c procedure (68, 69, 72, 75, 84, 133) is the simplest approach to the electromagnetic flowmeter technique (see fig. 26). A constant magnetic field is used from either an electromagnet or a permanent magnet. The pole pieces of the magnet should be constructed in such a way that the gap can be adapted to the vessel size and the pole faces are large enough to insure a uniform magnetic field across the entire vessel segment. The field strength should be as high as possible, e.g., 1000 to more than 10,000 gauss. In case of 10,000 gauss and a vessel diameter of 0.5 cm, a flow

rate of 1 ml per sec will generate a flow-signal voltage of about $0.25 \cdot 10^{-3}$ volts (equation 14). In the ascending aorta or pulmonary artery trunk, signals of several millivolts can be recorded at flow peaks. Non-polarizable electrodes are indispensable. Zn-ZnSO₄ electrodes are useful; calomel half cells give still more satisfactory results [Katz & Jochim (72); Jochim (68)]. The electrodes are connected to the vessel wall by wicks soaked in saline-agar solution or by saline-agar filled glass tubes. Also Ag-AgCl electrodes are recommended (33). Furthermore, the vessel's diameter and cross-sectional area must be kept constant throughout the measurements. The best way is to use a rigid sleeve of insulating material (76). The size of the sleeve should be carefully chosen so that the vessel is narrowed down to that diameter which would be reached if the blood pressure fell to the lowest level expected during the experiment. This moderate constriction will not essentially interfere with the hemodynamic conditions, nor will the rigid sleeve give rise to pulse-wave reflections if it is not longer than about 1 cm. The tips of the saline connections to the electrodes are contained in two small holes placed in the sleeve wall at right angles to the vessel axis and to the lines of magnetic force. The sleeve also assures a fixed position of the vessel relative to the magnet and protects the exposed vessel from drying as well as from undesired contact with neighboring tissues. To permit introducing the vessel, either the sleeve has a small longitudinal slot, or is composed of two halves which are joined together around the vessel. If the flow-signal voltage picked up by the electrodes is high enough, it can be directly recorded by a string galvanometer (75, 133). However, d-c amplifiers are generally employed (33, 64, 68, 110, 128, 134), or the input voltage is converted into alternating current by a mechanical chopper (72, 76), and a capacitance-coupled amplifier may then be used. The over-all frequency response of the amplifier system and recording galvanometer should be uniform up to at least 50 cps.

The base line is assessed during the experiment either by clamping the vessel distal to the site of measurement or by de-energizing the magnet. See also (32). Calibration is performed by perfusing the excised vessel or the vessel in situ with blood or saline solution at known flow rates. Because of the strictly linear calibration curve, it is sufficient to determine, in addition to the zero point, only one point corresponding to a flow rate near the upper limit of the range under investigation. The calibration can also be done using a nonsteady flow: a known quantity of

fluid is injected into the vessel by means of a syringe, and the course of the corresponding flow signal is recorded. Thus the mean flow rate and the mean flow signal can be calculated from the known injected volume and the time and deflection as recorded on the tracing (73).

In spite of its theoretical simplicity, the d-c procedure has been widely abandoned because of several practical drawbacks. The magnet and most types of nonpolarizable electrodes are rather bulky. In the case of flow measurements on small vessels, the flow-signal voltage is very low so that high-gain d-c amplification with its inherent difficulties is required and changes of the electrode potential will cause drift of the base line. The results of Richards & Williams (110) and of Inouye *et al.* (65) show that, in spite of utmost care, such difficulties are present even in the application of the d-c procedure to the dog's carotid and femoral arteries. By improving the electrodes and using modern stabilized d-c amplifiers, however, satisfactory short-time recordings of the flow in the descending aorta of the dog have been made possible [Feder & Bay (33)]. As to vessels close to the heart, cardiac action potentials may be picked up by the electrodes in addition to the flow signal.

The a-c modification [Kolin (76, 77)] is characterized by the use of an alternating magnetic field which is generated by energizing the coils of the electromagnet with sinusoidal alternating current:

$$B = B_0 \sin \omega t \quad (15)$$

where B_0 = amplitude of magnetic flux density; $\omega = 2 \pi f$; f = frequency; t = time. The flow signal picked up by the electrodes is, therefore, an a-c voltage which is strictly in phase with the a-c magnetic-field strength. The amplitude of the flow-signal voltage is further proportional to the average instantaneous flow velocity or flow rate:

$$E_f = BD\bar{v}_A \cdot 10^{-8} = B_0 D\bar{v}_A \cdot 10^{-8} \sin \omega t \text{ volts.} \quad (16)$$

This means that an amplitude-modulated flow signal is delivered so that the well-known advantages of a carrier-frequency operation result, especially with the use of a-c amplifiers which permit higher gain and greater stability than d-c amplifiers. A further advantage of the a-c modification is that the flow-signal voltage can be picked up by simple metal electrodes, such as platinum, gold, silver, or stainless steel. As much higher gain is obtainable than by d-c amplifica-

tion, lower flow signals are permissible. The magnetic field strength and the magnet size may be greatly reduced, and the method can therefore be applied to very small vessels. Since miniaturization of the magnet-sleeve-electrode assembly is possible, the devices may even be adapted for chronic implantation. Finally, any spurious potentials which change in time at a much lower frequency than that of the carrier used can be excluded from registration by appropriate circuitry of the amplifier and demodulator (123). Usually a carrier frequency of a few hundred cycles per second will be high enough to cancel cardiac action potentials.

A sufficiently high carrier frequency should be chosen for a more important reason (123). If Δf is the highest frequency of the flow oscillations to be recorded and f is the carrier frequency, a pass band reaching from $(f - \Delta f)$ to $(f + \Delta f)$ has to be amplified while by the demodulation and output filtering the carrier is suppressed and a filtered output signal of a frequency range from 0 to Δf is obtained for registration. According to generally known principles, f must be higher than $2\Delta f$. In case of flow recording, Δf is usually about 50 cps (35); in special cases, Δf may be higher, say up to about 100 cps. Therefore, f should be above 200 cps, i.e., 300 to 500 cps. On the other hand, f should not be higher than necessary because particular difficulties (see below) will increase with rising frequency. A carrier frequency of about 400 cps will permit reaching an adequate frequency response of the flow signal without undesired nonmodulated signals such as those of the ECG. Standard line current ($f = 60$ or 50 cps), which was used in the earlier developmental stages of the a-c method, may be successfully used to energize the magnet when a smaller frequency range is sufficient (89, 111, 132).

A particular difficulty hampering the a-c sine-wave procedure has been hardest of all to overcome. The electrode leads, the electrodes, and the vessel segment lying between them form a transformer loop in which an a-c voltage is induced by the alternating magnetic field. This spurious voltage, which is commonly called "transformer component" or "transformer emf," is proportional in strength to the rate of change of the magnetic field strength (dB/dt) and also depends on the configuration of the effective transformer loop. It follows from equation 15 that $dB/dt = B_0\omega \cdot \cos \omega t$, and the transformer component will be $E_t = KB_0\omega \cdot \cos \omega t$, where K = coefficient related to the loop configuration. Thus we get the actual a-c voltage E_i

fed into the amplifier input (66, 80) as the sum:

$$E_i = E_f + E_t = B_0 \cdot 10^{-8} (D\bar{V}_A \sin \omega t + K\omega \cos \omega t) \text{ volts.} \quad (17)$$

Obviously, E_t leads in phase by 90° and will rise in amplitude with increasing frequency of the magnet current. Additional spurious a-c voltage may also be created by the stray capacitance of the magnet coils on the one hand and the vessel, electrodes, and leads on the other; it can be minimized by electrostatic shielding of sleeve and leads and by using a balanced push-pull or differential amplifier with high common-mode rejection.

Various designs have been worked out [for a survey see (123)] for eliminating or at least minimizing the transformer emf. The most important of these are as follows: *a*) A special variable-phase transformer is fed by the magnet current; the output of this transformer is arranged in series with one of the electrode leads so that cancellation of the "transformer component" is wrought by an opposite-phase emf delivered by the phase transformer (Kolin). Complete cancellation is impossible because of wave form distortion due to non-linearity of magnetic-core material. *b*) Cancellation voltage is derived from a special pickup coil wound around the magnet core (18, 112, 113). Complete cancellation is possible with this refinement by careful adjustment of a potentiometer. *c*) A split-lead method (28) can be used. It is a modification of *b* in which one electrode lead is split; the halves are placed on either side of the magnet core and are joined by a potentiometer. This arrangement also makes cancellation possible. *d*) An auxiliary pickup coil can be arranged at the sleeve (80) in external-magnet devices. *e*) Careful orientation of both electrode leads can form a non-inductive loop (66, 80, 82). This technique is mainly applied in magnet-sleeve units. It permits approximate cancellation. Complete cancellation can be achieved by additional phase-sensitive demodulation (82). *f*) Demodulation with phase discrimination should, theoretically, permit separating E_t from E_f to obtain the latter only, since they differ in phase by 90° . Simple demodulators consisting of half-wave or full-wave rectifiers cannot provide any separation of signals by their phase. Kolin (77) first applied optical phase discrimination on the screen of an oscilloscope. James (66) suggested electronic phase discrimination in a-c flowmeters. Continuous phase-sensitive demodulation or discontinuous discrimination by gating

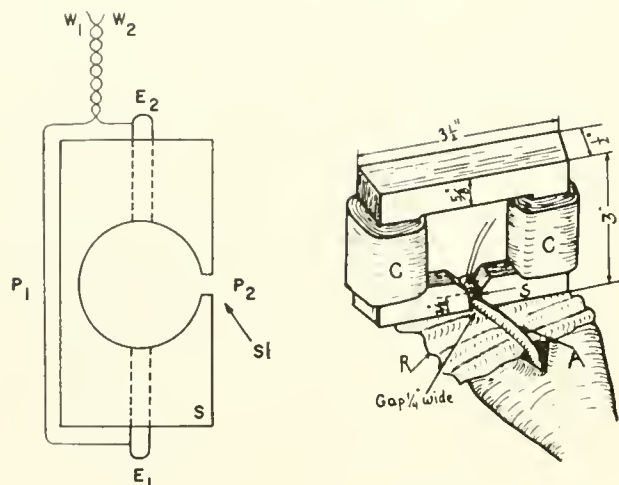


FIG. 27. A-C flowmeter for application on exposed arteries (Kolin). *Left*: cross section of sleeve *S*. *E*₁, *E*₂, electrodes; *P*₁, *P*₂, location of magnet pole pieces; *W*₁, *W*₂, braided electrode-lead wires; *S*₁, slot for insertion of vessel. *Right*: total view with artery *A*. *C*, magnet coils; *S*, sleeve; *R*, rubber sheet for insulation of tissues from magnet core. [From Kolin (82).]

and sampling the amplified flow signal at the peaks of $B(B = B_0; dB/dt = 0)$ have been employed (3, 83, 132) and recommended in combination with mode *e*. Another way, that of phase detection at the points ($B = 0; dB/dt = \text{maximum}$) was described by Olmstead & Aldrich (99) and found to yield a stable base line. *g*) Abandoning the sine-wave type and using rectangular wave shape led to the square-wave flowmeter which will be described below.

Cancellation of the transformer emf E_t is closely related to the assessment and stability of the base line. Only if E_t is eliminated or compensated for, does switching off the magnet current render a true zero-flow reading as is obtained by occluding the vessel while the magnet is energized (82).

Although there is the possibility that zero changes occur as a result of changes in the position or conductivity of the vessel wall at the site of measurement (23), such difficulties are not a necessary accompaniment of the application of the a-c procedure to intact vessels as shown by recent reports (82).

Numerous models of a-c flowmeters have been built, some of which may, as examples, be mentioned here. Figure 27 shows an early a-c device (Kolin) applicable to exposed and unopened arteries. The simplicity of sleeve and electrodes as compared with d-c devices is obvious. Special sleeves with imbedded electrodes have been used for chronic implantation (80, 81). After recovery from the operation, the animal is

placed in the field of an external a-c magnet. Auxiliary coils attached to the sleeve deliver induced a-c signals which are used for calibration, orientation, and compensation. The further development (see 81, 82) produced miniaturized devices consisting of magnet-sleeve assemblies constructed in compact units and cast in acrylic plastic. These provide a fixed orientation between vessel and magnet in chronic-implantation experiments. Units weighing 5 to 10 g have been successfully built which reach flux-density peaks (B_0) of 200 to 500 gauss at a carrier frequency of 400 cps. For chronic implantation around small arteries of diameters down to 1.5 mm or less, subminiature units of still lower weight are described. As to the skillful manufacturing of these designs see (82) and figure 28.

The miniaturization of the a-c flowmeter is made possible by specially tuned amplifiers (400 cps) characterized by extremely high gain and low noise (82, 83). Input signals of $1 \mu\text{v}$ are measurable at a noise level of less than $0.2 \mu\text{v}$. The high amplifier gain allows the use of coreless coil-sleeve units for implantation around large vessels of diameters greater than 1 cm, e.g., aorta of dog (81, 82). A very low magnetic field strength ($B_0 = 10$ gauss) is sufficient in these cases. Core magnets are also used in a-c devices implantable about the aorta of dogs (98).

As already mentioned, one of the ways of eliminating the transformer component consists in avoiding the sinusoidal wave shape in a-c flowmeters. Thus, a group of "signal-separating" a-c flowmeters (126) has been created, the most important model being the square-wave type developed by Denison *et al.* (22, 23, 126). The magnet is energized by an alternating current following a rectangular time course

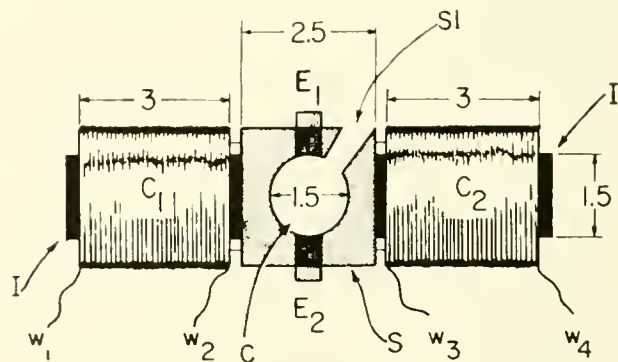


FIG. 28. Subminiature flowmeter (Kolin). Dimensions in mm. *I*, iron cores; *C*₁, *C*₂, magnet coils; *w*₁-*w*₄, coil-terminal wires; *S*, sleeve; *C*, sleeve channel for vessel; *S*₁, slot; *E*₁, *E*₂, electrodes. Leads and coating of the unit with acrylic plastic are not shown. [From Kolin (82).]

so that, on the plateaus, the field strength ($B = B_{max}$) is constant and, because ($dB/dt = 0$), no transformer emf is induced. During these periods, the system behaves like a d-c flowmeter while the advantages of a carrier-frequency a-c procedure are achieved by the fact that $B = B_{max}$ in each first half cycle and $B = -B_{max}$ in each second half cycle. Therefore two flow signals of opposite polarity are delivered in each cycle which are picked up by simple metal electrodes, amplified by an a-c amplifier, and then converted to congruent polarity by the discriminating demodulator. It is obvious that spurious input signals which do not change their polarity synchronously with B , such as ECG, can be cancelled out if the carrier frequency is high enough. During the short time intervals of magnet-field reversal, dB/dt is very large so that high spikes of transformer emf may be picked up by the electrode circuit. This emf can be reduced by the aforementioned split-lead method. However, the preferred way to eliminate the transformer emf consists in blocking the amplifier during the field reversals. Satisfactory separation of the flow signal from unwanted a-c voltages is therefore, at least in theory, quite possible. The electric circuitry is more complex than for sine-wave flowmeters. Figure 29 shows the principle of operation. *A* is the idealized rectangular time course of the magnetic field strength. *B* shows the assumed course of blood flow as well as the input signal which consists of the amplitude-modulated flow signal and the transformer spikes. The blanking periods *C* indicate the time intervals during which the amplifier is blocked. Periodic gaps in signal voltage due to the blanking operation are filled out by prolonging the duration of the voltage level reached immediately before the beginning of each blanking period ("filler voltage"). The demodulated voltage shown in *D* has a steplike appearance which is, for clarity, exaggerated in figure 29 and will be smoothed by filtering. For the block diagram of the circuitry see figure 30. The low-pass inverse feedback between output of spike-blanking circuit and input of pre-amplifier raises the lower frequency limit for suppressing the ECG.

The method is used for flow recording on intact vessels in human surgery as well as in acute and chronic-implantation experiments on animals (see fig. 31). Flow measurements in extracorporeal devices have been described (126).

The heat produced by the magnet-coil current is relatively great, since the electric power used to obtain the rectangular wave current is greater than that

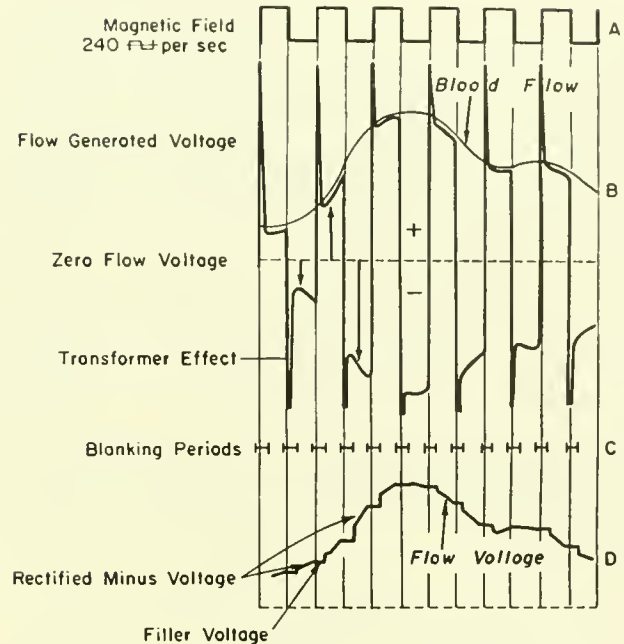


FIG. 29. Principle of operation of the 240 cps square-wave flowmeter of Denison and Spencer. For description see text. [From Spencer & Denison (126).]

needed for an equally effective sine-wave current. In addition, a higher ampere-turn value is needed to saturate the core material and make the magnetic-field plateaus flat. Even so, it is difficult to make these plateaus perfectly flat so that a small transformer emf may be still effective during the sampling periods. A minor difficulty is the influence of the blood hematocrit on the flowmeter's sensitivity, the nature of which is not understood.

A square-wave flowmeter similar to the 240-cps model of Denison and Spencer was also described by Ferguson & Wells (34) while Abel (1) developed a 400-cps chopper-operated square-wave meter. Shirer *et al.* (123) built a 480-cps square-wave device possessing a frequency response up to 150 cps. The reader may refer to their thorough considerations of problems of carrier frequency, filtering, gating, and noise. Besides rectangular or trapezoidal wave shape, Spencer and Denison suggests a sawtooth-like time course of the magnetic field (126).

At the present state of flow recording technique, the electromagnetic method is a superior procedure. Any decision whether the preference should be given to the sine-wave, the square-wave or another wave-shape type must await further development.

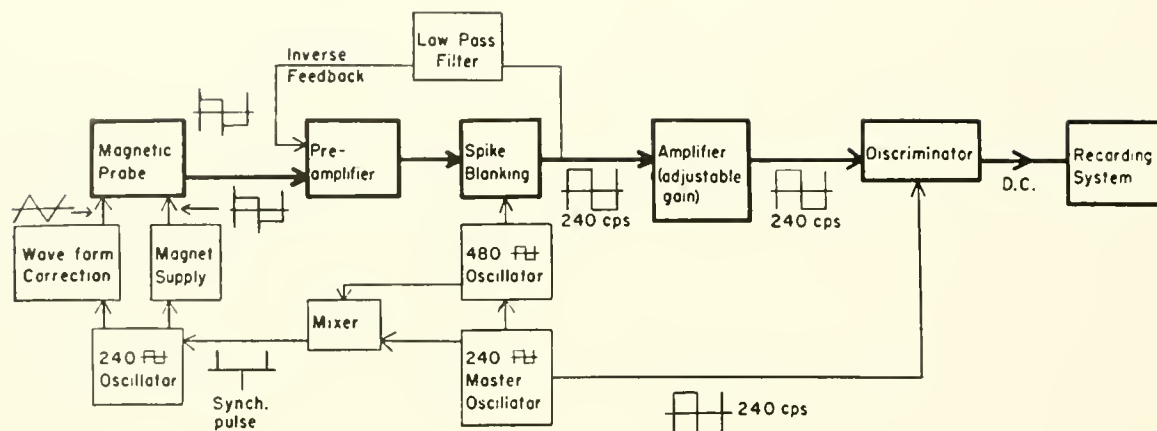


FIG. 30. Block diagram of the square-wave flowmeter circuits required to energize the magnet, eliminate spurious emfs, amplify the flow signal, and convert it to direct current. [From Spencer & Denison (126).]

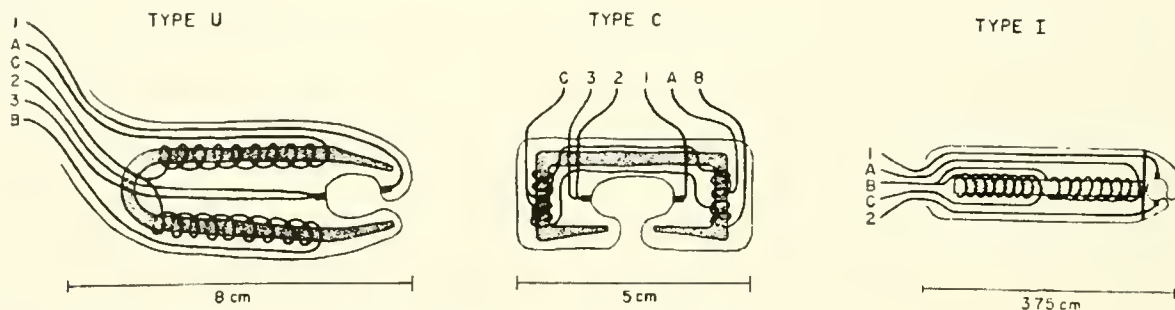


FIG. 31. Three types of magnet-sleeve units used in the square-wave flowmeter technique: Type U (horseshoe) mainly employed in surgical measurements, type C for implantation about large vessels, type I for small vessels. A, B, C, magnet-coil terminals; 1, 2, 3, electrode leads; 2, 3, split lead. The units are imbedded in plastic cast. [From Spencer & Denison (126).]

ULTRASONIC FLOWMETERS

The measurement of blood velocity by recording sound-transit times upstream and downstream within a vessel segment of small length offers, in principle, several important advantages. The device placed around the vessel is very lightweight and simple in construction. The vessel remains intact, and there is no interference with the blood flow or pulse wave except that effected by a short rigid sleeve causing a moderate constriction. The calibration curve can be made to be a straight line passing through the zero point with equal slopes for forward and backward flow. The signals obtained can follow the most rapid changes of the instantaneous blood velocity occurring in the circulation. However, in contrast to the simple device applied to the vessel itself, very involved electronic equipment is required to detect and evaluate the extremely small effects exerted by the flow on

the sound transit times. Since sound velocity in blood is about $1.5 \cdot 10^5$ cm per sec, the time required for traveling over a distance of 1 cm is about 7μ sec. If the blood is moving at the velocity v along the direction of sound propagation, the apparent sound velocity measured between two quiescent points is $(c - v)$ or $(c + v)$ for upstream or downstream sound direction, respectively. A flow velocity of 1 cm per sec will therefore change the sound transit time (7μ sec/cm) by about $\pm 5 \cdot 10^{-11}$ sec. Thus utmost precision is necessary if differences of such a minute order of magnitude are to be measured with sufficient accuracy, and the admirable advances made in this field to date are based on very difficult and detailed work. The development of ultrasonic blood flowmeters has been carried out mainly by two groups using different approaches.

Haugen *et al.* (58) and Herrick & Anderson (59), modifying the design of Kahnus, developed a phase-

difference procedure. Cylindric ceramic "transducers" are placed about 1 inch apart around the vessel wall. They are arranged to transmit and receive ultrasound ($f \cong 400$ kc/sec) alternately upstream and downstream at a rate of 75 per sec. The phase differences between the signals received upstream and downstream are detected by phase meters and used as a measure of the differences (Δt) between the upstream and downstream sound transit times:

$$\Delta t = L \left(\frac{1}{c-v} - \frac{1}{c+v} \right) \cong \frac{2Lv}{c^2} \quad (18)$$

where L = distance between the transducers. Since the phase angle $\Delta\Phi = 2\pi f \cdot \Delta t$, we get:

$$\Delta\Phi \cong \frac{4\pi fLv}{c^2} \text{ radians.} \quad (19)$$

In the present design (31, 59) where $f = 4 \cdot 10^5$ cps and $L = 2.5$ cm, a blood velocity of 1 cm per sec will cause a phase angle of about $5 \cdot 10^{-4}$ radians or 0.03° . The output signal of the apparatus is proportional to $\Delta\Phi$. Due to undesired phase differences, assessment of the base line remains a difficult problem. An improvement was achieved by introducing an automatic phase-shift control. The authors succeeded in constructing a reliable recorder of extracorporeal blood flow. Preliminary findings indicate that satisfactory results may ultimately be attained on vessels in vivo. For this purpose, the switching rate of the transducers has to be increased, and the time constants of some of the circuits have to be reduced (59).

Franklin *et al.* (43-45) made use of the pulse technique in detecting and evaluating the differences in upstream and downstream sound-transit times. As seen in figure 32, their flow-sensing element consists of a short (1-3 cm) Lucite cylinder which is split longitudinally and mounted snugly about the vessel. The sound is transmitted and received by two barium titanate crystals placed on the vessel wall diagonally from each other across the vessel lumen. The crystals are set to function alternately 800 times per sec as transmitter and receiver. The respective transmitter crystal is pulse-excited at a repetition rate of 12,000 per sec so that it will, during each switching period of $1/800$ sec, give off a train of ultrasound bursts at its resonant frequency of 3 mc per sec. These waves travel through the adjacent vessel wall, the blood, and the opposite vessel wall to reach the receiver crystal. In the next switching period, the functions of both crystals are exchanged so that in every $1/400$ th sec a train of upstream and a train of downstream transits are available for determination of Δt . Equation 18 is

applicable to this device if L is replaced by $d \cdot \cos \theta$ where d = length of diagonal between the crystals and θ = angle between diagonal and vessel axis. The transit-time voltage converter generates a ramp voltage showing a strictly constant slope of 40 volts per μ sec. This ramp voltage is started at the beginning of every sound transmission, and its ascent is abruptly stopped when the respective receiver crystal begins to be excited by the sound, so that the amplitude of the ramp voltage is proportional to the sound-transit time. It is obvious that, due to the blood flow, the upstream ramp-voltage amplitude is greater than the downstream one. This difference amounts to 4 mv per 10^{-10} sec and is detected by the voltage comparator which delivers a 400 cps square-wave voltage with an amplitude proportional to the difference between the upstream and downstream ramp-voltage amplitudes. Finally, a synchronized detector converts the square wave into a d-c voltage, which indicates the instantaneous magnitude and direction of the blood velocity. The device possesses satisfactory sensitivity to flow and high stability of the base line. The stability is achieved mainly by using whenever possible, only one functional unit or channel for detecting differences in time or voltage of consecutive events. Due to the carrier frequency of 400 cps, the apparatus is capable of an excellent frequency response to pulsatile blood flow. As far as seen from the tracings published in reduced scale, the flow patterns recorded on blood vessels of different sizes in vivo are very similar to those obtained by the electromagnetic method. In addition, the simultaneous application of several or many ultrasonic meters is possible without any mutual interaction (44). One is inclined to predict that this kind of versatile flowmeter is on its way toward becoming a favorite instrument in cardiovascular research. The same may happen regarding the application of ultrasound to the recording of instantaneous dimensional changes of organs [Keidel (74); Edler & Hertz (27); Rushmer *et al.* (115)].

However, it seems that the possible dependence of the calibration of the ultrasonic flowmeters on the velocity profile has not yet been duly considered. The sound passes from the transmitter to the receiver crystal on a diagonal path which crosses the streamlines of moving fluid at the angle θ (see fig. 32). It may be assumed that only the streamlines crossing this diagonal will cause flow-related changes of the sound-transit times. Furthermore, the relative velocity distribution taken over the diagonal may be considered to equal that taken over the vessel's diameter or radius. This means that the device will indicate the

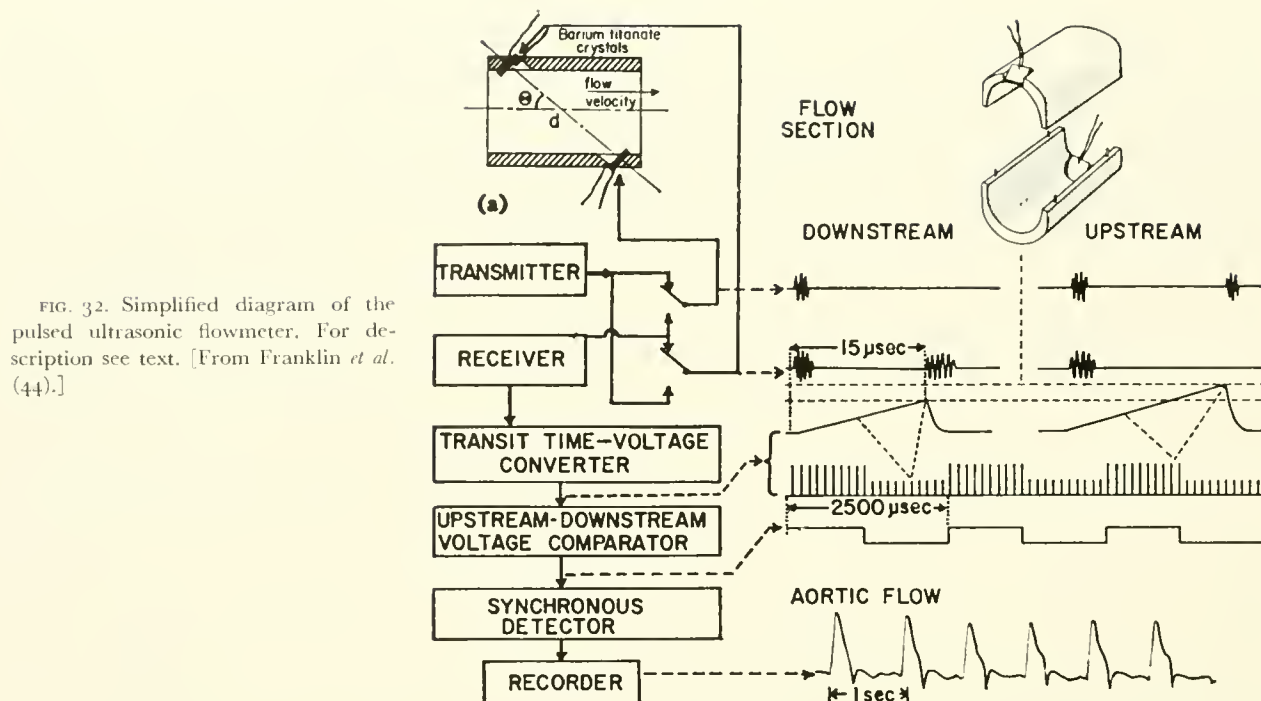


FIG. 32. Simplified diagram of the pulsed ultrasonic flowmeter. For description see text. [From Franklin *et al.* (44).]

velocity \bar{v}_R averaged over the vessel's diameter or radius, and that therefore the calibration in terms of the flow rate varies with the velocity profile. On the other hand, corrections might be brought about by additional effects, such as some flattening of the velocity profile by the slight constriction of the vessel caused by the sleeve, and the fact the ultrasound beam reaching the receiver is not in the form of a line, but of a band. Rushmer describes the calibration of his ultrasonic flowmeter as being independent of the velocity profile within ± 5 per cent (44). With respect to the growing importance of this flowmeter type, the problem should be reconsidered both theoretically and practically.

TRAVELING MARKERS

Estimations of blood velocity can be made by observing, continuously photographing, or filming the movement of any substance which acts as a distinguishable marker traveling with the blood stream. In most cases, such a procedure will allow only single short-time recordings which can be repeated at intervals. The marker may be represented by dye, by a drop of fluid nonmiscible with the blood [see (54, p. 60) (50, p. 116)], by radiopaque material for cineradiography (2, 7, 24, 90, 106), or by a gas bubble.

Even the blood's own corpuscles can be used as markers (63), and the progress of blood columns differing in oxygen saturation may be assessed photoelectrically (85) (cf Chapter 18, vol. I, of this *Handbook*). Foreign substances are usually injected into a side branch and then observed through the wall of the vessel under investigation. In contradistinction to flowmeters in the proper sense, the use of traveling markers does not give the volume flow at a fixed site; it rather gives a function of time and space since the mark changes position during the measurement. In case of relatively small displacements, the change in the site of measurement may be neglected. Dyes are particularly useful for the study of the flow course in small vessels. Valuable results were obtained with China ink and high-speed cinematography on pulmonary capillaries (130) and on very small arteries of the rabbit ear (136).

In a carefully elaborated procedure, McDonald (91-93) studied the flow pulse in the rabbit aorta and in peripheral arteries of the dog by filming the movement of injected gas bubbles through the translucent vessel wall. Gas embolism was avoided by using pure oxygen instead of air. An injected gas bubble travels at a velocity quite near to the average blood velocity \bar{v}_A if the bubble is spherical and just fills the lumen completely. Smaller spherical or larger cylindrical bubbles will run faster. High-speed cinematography

at about 1000 frames per sec is used, the exposure of each frame being 200 μ sec. For evaluation, the distance-time relation is plotted from the projected film, and the time course of the velocity is obtained by graphic differentiation. McDonald's work is of particular significance regarding hemodynamics because his simultaneous recordings of the pressure gradient make possible hydrodynamic flow calculations and comparison of the calculated flow pattern with that determined by cinematography.

MISCELLANEOUS METHODS

Röckemann (114) tried to measure the blood velocity by means of electrolytic polarization taking place at electrode surfaces which are in contact with the streaming blood. A stable calibration, however, is not obtainable for this method.

The application of nuclear magnetic resonance to blood flow measurements was described almost simultaneously by Buchman and by Singer in 1959. Buchman's device (17) passes protons, the spin axes of which have been aligned, through a varying magnetic field. Energy is required to bring them into resonance. Thus the absorbed energy is a measure of the number of protons passing per time unit, and hence, is proportional to the flow rate. Singer (124) uses several methods based on nuclear magnetic resonance. In one of the procedures, the nuclear relaxation time of the protons in the water of streaming blood is measured and compared with the relaxation time of those in stopped blood; only single determinations of relative values are obtained. By another procedure described by Singer, absolute flow velocities can be recorded at short time intervals. The nuclei are perturbed by the 60 mc per sec field of a transmitter coil, and the time required by the nuclei to reach a second

detecting coil is measured. Singer also considers nuclear or electron magnetic resonance as a tracer detection system. It seems worthwhile to carry on the development of these methods since they are applicable to unopened vessels, even from outside through the intact skin.

ADDENDUM

Since completion of the manuscript, several papers have been published which should be referred to:

ELLIOTT, S. E., J. I. E. HOFFMAN, AND A. GUZ. An electromagnetic flowmeter for simultaneous measurement of ventricular ejection in the conscious animal. *Digest of 4th Intern. Conf. Med. Electronics*, New York, 1961, p. 150. Coreless electromagnetic flowmeter units were implanted around the ascending aorta and pulmonary artery of the dog. A-c sine-wave type, 400 cps. Some magnetic interference between both units was observed.

YANOF, H. M. A New Trapezoidal-wave Electromagnetic Blood Flowmeter and Its Application to the Study of Blood Flow in the Dog (Ph.D. thesis). Berkeley: Univ. of California, 1960. Description of circuitry. 1000 cps. Adjustment of minimum transformer emf by an additional ferrite slug.

WYATT, D. G. Problems in the measurement of blood flow by magnetic induction. *Phys. in Med. Biol.* 5: 289, 1961. Thorough examination of performance, and possible error sources in the application, of electromagnetic flowmeters.

ZARNSTORFF, W. C., AND C. A. CASTILLO. An ultrasonic flowmeter. *Digest of 4th Intern. Conf. on Med. Electronics*, New York, 1961, p. 86. Stable phase-difference device appropriate for recording of blood flow in unopened arteries.

FRANKLIN, D. L., D. W. BAKER, AND R. F. RUSHMER. Pulsed ultrasonic transit time flowmeter. *IRE Trans. on Bio-Med. Electronics BME-9*, 44, 1962. Diagrams of electronic circuitry.

HIGASHI, K. (ed.). Platinum blood flowmeter. *Research Inst. Appl. Elec., Hokkaido Univ., Monograph Ser. No. 10*, 1962. Contains several papers by M. Mochizuki and co-workers on the relation between polarographic current for oxygen and the flow velocity. Application to flow measurement in arteries. Catheter-tip method. Calibration curve concave to flow abscissa at low velocities and linear at higher velocities.

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The circulation through the skin

A. D. M. GREENFIELD

*Department of Physiology, The Queen's University of Belfast,
Belfast, Northern Ireland*

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INTRODUCTION

THIS SECTION deals principally with the circulation through human skin, since this has been so frequently and carefully studied, mostly in unanesthetized subjects. In selecting references no attention has been in general paid to priority of discovery. Papers have been chosen for the completeness of the information they contain, for the value of their bibliography, and very often because the work is personally known to the present author. A wider bibliography will be found in several excellent monographs and reviews (1, 19, 22, 44, 115, 119, 139, 148, 152, 155, 165, 176, 187, 193).

The great bulk of observations relates to the circulation through the skin of the extremities, and particularly of the digits. Here the striking features are, firstly, the very great variability of the blood flow under different circumstances, greatest in the tips

FIG. 1. Projection drawing ($\times 95$) of a group of anastomoses in the nail bed of the toe. The artery crosses the center of the drawing and gives rise to 12 thick-walled anastomotic branches. The thin-walled venous terminations of several are shown. [From Grant & Bland (99).]



of the fingers where the maximum flow is probably between 100 and 200 times the minimum (42), and secondly, the fact that in normal persons the blood flow to the skin is greatly in excess of its metabolic requirements, being chiefly determined by the need to maintain thermal balance (82). This lavish circulation is, no doubt, valuable in the repair of trauma and wounds to which the skin is especially exposed. Perhaps because of methodological difficulties, there is very little information about the circulation through other areas of skin, but it is almost certainly much less reactive than that through the extremities.

Arrangement of the Blood Vessels of the Skin

The skin is supplied with a profuse system of capillary loops which rise in the papillae of the corium and return to enter a subpapillary venous plexus. The vessels of the latter are large and have thin walls, and it is probable that when distended they contain a

very large proportion of all the blood in the skin. There are rich capillary networks around the sweat glands, at the base of hair follicles, around the sebaceous glands, and in the nail bed and nail fold.

In the skin of the extremities a special and prominent feature is the large number of arteriovenous anastomoses (50, 147). These are coiled channels (fig. 1) with thick muscular walls and a lumen which in the dilated state is between 20 and 70 μ in diameter, the average being 35 μ . They are abundantly supplied with nerve endings, and a high concentration of cholinesterase has been reported around them (28, 124, 151). They directly connect arterioles and venules in the dermis at the level of, or a little superficial to, the sweat glands. They are most numerous in the nail bed, numerous at the tips of the digits, less numerous on the palmar surface of the phalanges, and almost absent from the dorsum of the phalanges. They are fairly numerous in the palm of the hand and sole of the foot, but are absent from the areas of the forearm and calf which have been examined.

TABLE 1. *Number of Anastomoses per Square Centimeter of Surface Area*

| | |
|---------------------------------------|-----|
| <i>Hand</i> | |
| Index finger | |
| Nail bed | 501 |
| Tip | 236 |
| Palm, 3rd phalanx | 150 |
| 2nd phalanx | 20 |
| 1st phalanx | 93 |
| Palm | |
| Metacarpo-phalangeal joint 3rd finger | 31 |
| Thenar eminence | 113 |
| Hypothenar eminence | 96 |
| <i>Foot</i> | |
| 2nd toe | |
| Nail bed | 593 |
| Pad | 293 |
| Sole, near heel | 197 |

These are nil for dorsal surfaces of fingers, toes, hand, and foot; flexor surfaces of lower forearm and lower calf of leg; lower half of ear. [From Grant & Bland (99).]

TABLE 2. *Percentage Composition by Volume of Parts of Human Limbs*

| | Hand | Foot | Forearm | |
|---------------------|------|------|---------|------|
| | | | A | B |
| Skin | 30.2 | 17 | 8.6 | 13.4 |
| Subcutaneous tissue | | 24 | 8.0 | |
| Fat | | 2 | | |
| Bone | 54.3 | 43 | 13.7 | 28.0 |
| Tendon | | | 6.1 | |
| Muscle | 15.5 | 14 | 63.6 | 58.6 |

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- Hand Average of 3 hands (2).
 Foot Average of 2 feet (12).
 Forearm A Average of 5 forearms (56).
 Forearm B Average of 3 forearms (2).

Table 1, from Grant & Bland (99), summarizes the distribution in the human. They have since been found in the human ear (164). Some observers (151, 163) have reported rather smaller numbers (20–25/cm²) than did Grant and Bland in the finger pad. They are numerous in the external ear of the rabbit, where their reactions have been carefully studied (98), in the ear of the cat and dog and in the feet of webfooted birds. Grant's (98) summary of the functions of the anastomoses is still valid, and applies to the human extremities as well as to the rabbit's ear: "The anastomoses serve two functions (a) local,

and (b) general. (a) It is mainly through their agency that the temperature of the ears is maintained when they are exposed to cold. (b) They are important factors in regulating of body temperature, aiding the dispersal of heat by allowing an enormous blood flow through the ears." (See also Chapters 27 and 37.)

Measurement of the Flow of Blood Through the Skin

The fingers and toes are composed largely of skin. Of the total flow through them, the greater part normally passes through skin, and total digital blood flow is often used as an index of digital skin blood flow (table 2). Digital flow may be directly measured by venous occlusion plethysmography (40, 95), a method which permits variation in the rate to be followed from one heart beat to the next, and even during a single beat. Flow may be estimated by calorimetry (148), a method which, because of the thermal capacity of the tissues, is incapable of following rapid changes in flow, but which conveniently integrates flow over a period of time. Calorimetry finds its most successful application in the digits, and the method has been rendered more versatile by the use of copper-tellurium heat flow discs (47).

In the more proximal parts of the limbs, the total blood flow depends a great deal on the circulation through tissues, especially muscle, deep to the skin. The flow through the skin can be deduced by comparing the total flow in a pair of segments in one of which the circulation through the skin has been suppressed by iontophoresis of adrenaline (71). More often, indirect indices of skin blood flow have been employed. If venous blood can be obtained from vessels exclusively draining skin, and if the oxygen usage of the skin is assumed to remain constant, changes in flow can be inferred from changes in the oxygen content of the blood (170). Measurements of the temperature of the skin have provided useful qualitative information in the proximal as well as in the distal parts of the limbs (100), but this temperature, as explained later, depends on so many other factors that it is a very imperfect index of skin circulation. It is incapable of following accurately rapid fluctuations in flow; if the circulation is completely arrested the temperature of the skin falls very slowly. A more sensitive index of blood flow is the change in thermal conductivity of the skin, which can be conveniently measured by a surface applicator containing two small plates, one of which is electrically warmed while the temperature difference

between the plates is recorded (114). The instrument does not, of course, distinguish between the effect of blood circulating through the local blood vessels of the skin, and blood flowing through nearby veins draining distal regions. The results cannot be quantitatively translated into measurements of blood flow, but the method retains its sensitivity over the wide ranges of flow for which measurement of skin temperature is of little help.

The rate of clearance of radiosodium from an injection site (130) probably depends on the rate of blood flow through those vessels which nourish the tissues, and is probably little affected by the rate of blood flow through, for example, arteriovenous anastomoses.

The capillary loops of the nail fold are among the most easily visualized in the living body, and they have been much observed (175).

TOTAL CUTANEOUS BLOOD FLOW. This quantity has not been measured with precision, but in a warm subject it is a considerable fraction of the cardiac output. Hardy & Soderstrom (112) by a study of deep and superficial temperature and heat exchange arrived at a blood flow through the skin of 278 ml per m² of body surface per min in a nude subject at rest at an environmental temperature of 35 C. Behnke & Willmon (29) measuring helium absorption through the skin under similar conditions arrived at a figure of 230 ml per m² per min. During generalized maximum cutaneous vasodilatation the total blood flow is presumably very much greater. Assuming, for example, a mean thickness of 1.2 mm, and a maximum flow of 180 ml per 100 ml skin per min, which has been reported in digits and inferred in the forearm, the flow would be 1200 ml per m² per min. Another estimate, based on skin conductance, is 2000 ml per m² per min (115).

Color of the Skin

The color of the skin due to tissue pigment is revealed by expelling the blood by local pressure. The additional color, due to circulating pigment, depends on the quantity, quality, and distribution of this pigment in the skin and subcutaneous vessels. It is not dependent on the rate of blood flow (139). Although it often happens that the skin contains more blood when the flow is fast than when it is slow, the amount of blood contained in the tissue and the rate at which blood flows through the tissue by no means run parallel to each other (54). Thus, the intensity

of the color indicates the amount of pigment present, and how near the surface are the vessels containing it. The hue is determined by the proportions of the various hemoglobin derivatives (oxy-, reduced, met-, carboxy- etc.) present.

Temperature of the Skin

The temperature of the skin in air depends partly on the rate of blood flow through it. It depends on the temperature at which the arterial blood arrives; that of the blood in the radial artery may be as low as 21.5 C in a subject who is not feeling unduly cold (25). It depends also on the rate of blood flow through both distal and subjacent tissues, on the activity of nearby muscle (101), on the rate of evaporation of sweat, on the temperature, humidity, motion, and pressure of the surrounding air, and on the exchange of radiant heat with the environment. It is clear, therefore, that there can be no simple relationship between the temperature of the skin and the rate of blood flow through it. The simplest relationship between the two quantities is probably found in the digits, examined in still air at a comfortable temperature. If the circulation is arrested, the fingers cool until their temperature settles near that of the air. With the circulation fully opened up, the temperature of the skin of the fingers comes to within about 1 C and that of the toes to within about 3 C of the temperature of the mouth. Between these extremes the relationship between flow and temperature is by no means linear. For example, in a room at 22 C, the temperature of the fingers may rise to 34 C when the blood flow is one quarter of the maximum, and to 36 C when the maximum is attained (55). In a room at 20.5 C, a skin temperature of 24 C corresponded with a blood flow through the toes of 3 ml of blood per 100 ml of toe per min; 29 C, with 10 ml, and 32 C, with more than 30 ml. Even flows of 70 ml do not cause the temperature to reach 34 C (75). This does not mean that the higher ranges of blood flow are always wastefully employed by the body, for in colder air, or in moving air, the difference in temperature to which the skin is raised by, and the difference in heat dissipation at, one quarter of the maximum flow and the maximum flow may be very considerable.

By far the greatest variations in skin temperature are found in the extremities, particularly the hands and feet in man, and the ears in the rabbit.

The temperature at the surface of the skin in thoroughly stirred water is essentially that of the

water. This follows because stirred water can convey heat to or from the surface at a rate which is very great indeed compared with the rate at which it can be conveyed to or from the surface by even the most profuse flow of blood through the tissues. If an insulating layer is formed, by allowing the water to stagnate, or by covering the skin with fabric, the skin becomes a point on the temperature gradient from the body core to the water. It assumes a temperature which depends on the ratio of the thermal insulation between the body core and the skin, and between the skin and the water. The thermal insulation between the body core and the skin is highly dependent on the state of the circulation. The circulation of the blood is the main means of transfer of heat between the body core and the periphery. The thermal conductivity of the skin is also highly dependent on the rate of blood flow through it (44).

RESPONSES OF SKIN BLOOD VESSELS TO PHYSICAL DISTURBANCES

Response of the Circulation Following Periods of Arrest or Insufficiency

REACTIVE HYPEREMIA. The circulation through the skin is very frequently arrested by local pressure; it is, for example, arrested in the sole of the foot while standing and in the parts of the hand supporting a heavy object. The skin is better able than most other tissues to survive fairly prolonged arrest of the circulation without permanent damage. It shows, conspicuously, the phenomenon of reactive hyperemia, by which is meant the bright red flushing (51) and increase in blood flow above the resting level (139) when the circulation is released following obstruction. This is a local change, and clearly depends upon a local dilatation of the blood vessels responsible for resistance to flow. The size and duration of the reactive hyperemia are related to the duration of previous arrest. Although some observations have indicated that the extra blood flowing during the period of hyperemia is closely similar to the amount that would normally have flowed during the period of arrest [debt and repayment hypothesis (142)] the correspondence is by no means always exact (83), the debt being frequently underpaid (157). Indeed, it is possible in the forearm, by gradually releasing the main vessel, to restore the circulation without any repayment of debt (35), the blood flow never exceeding the resting level.

Reactive hyperemia is most readily demonstrated when a limb is warm; it was found by Lewis & Grant (142) to be much reduced in a cooled part. Thus following arrest of the circulation for 5 min, Catchpole & Jepson (47) found average peak flows of 3.05 ml per 100 ml per min while the hand was immersed in water at 15 C, 6.8 ml at 20 C, 9.8 ml at 25 C, and 19.8 ml at 30 C.

Bier (33, 34) demonstrated in 1897 that reactive hyperemia is independent of nervous connections with the central nervous system. While amputating limbs he first divided the nerves and flesh, leaving the main artery and vein intact. Occlusion of the artery was followed, on release, by the usual hyperemia. Lewis & Grant (141) observed that skin which had long been anesthetized, as a result of old standing lesions of the main nerves, flushes uniformly with the adjacent skin still possessing normal innervation. In a chronically denervated and wasted forearm, the peak blood flow during reactive hyperemia was found by Eichna & Wilkins (73) to be 26 per cent greater, in relation to the volume of the part, than in the normally innervated arm. Similar observations on four other cases have been made by Duff & Shepherd (70). The height and the duration of the reactive hyperemia were found by Freeman (83) to be similar in the normal and the chronically sympathectomized hand. The reaction seems, therefore, to be independent of all nervous elements which degenerate following section of peripheral, somatic, and autonomic nerves.

The commonly observed rough correspondence of debt and repayment has suggested that a chemical substance may accumulate during circulatory arrest, and act as a vasodilator. Histamine has been found in the venous blood following arrest of the circulation (14), but in the forearm antihistamine substances do not influence the hyperemia following brief arrest, though they somewhat reduce that following more prolonged arrest of the circulation (69).

There is some evidence that the lowered pressure in the resistance vessels during circulatory arrest may lead to a relaxation of their muscular tissue, perhaps by a local mechanism. Thus Wood *et al.* (194) and Patterson (158) have found that reactive hyperemia in the forearm is reduced if the blood vessels are packed with blood, thus maintaining a high transmural pressure during the period of arrest of the circulation.

Present evidence suggests that reactive hyperemia depends on local chemical and physical changes,

which may contribute in varying proportion according to the circumstances.

HYPEREMIA AFTER PROLONGED INSUFFICIENCY OF THE CIRCULATION. A hyperemia, with the blood flow several times the normal level and lasting for some weeks, is seen in the feet of some patients after the relief of chronic arterial obstruction by an arterial graft (86). The mechanism of this hyperemia and its relationship, if any, to reactive hyperemia is not yet known.

Responses of Skin Vessels to Changes in Transmural Pressure

Measurements of the circulation through the finger have led Burton (43) and co-workers to conclude that in the resistance vessels there is an unstable equilibrium between the tension in the wall and the transmural pressure. If the transmural pressure falls below the "critical closing pressure," the value of which depends on the state of activity of sympathetic vasomotor nerves, the vessels close completely and arrest the flow of blood. This behavior of the vessels has been independently confirmed in the finger tip by Roddie & Shepherd (167).

Calorimetric measurements on the hand (53) and toes (52) indicate that when the transmural pressure is progressively increased beyond the normal value (as by local exposure to subatmospheric pressure) the resistance vessels at first are passively dilated. At somewhat higher pressures they react by active contraction of their walls and may become narrower than normal; this is a form of autoregulation of the skin circulation, the purpose of which may be to assist the antigravity defenses of the body rather than to maintain constancy of the skin blood flow.

Effect of Local Temperature on the Skin Circulation

The effects of local temperature on the skin circulation are of great importance, because the skin is normally exposed to a greater range of temperatures than any other part of the body except perhaps the upper end of the alimentary canal. In the latter, exposure to extremes of temperature is brief, but in the skin it may be prolonged.

A great many observations have shown that the circulation through the skin is greatly influenced by local temperature. The exposure of any part of the body to a change of temperature probably causes some alteration to the circulation in all other parts,

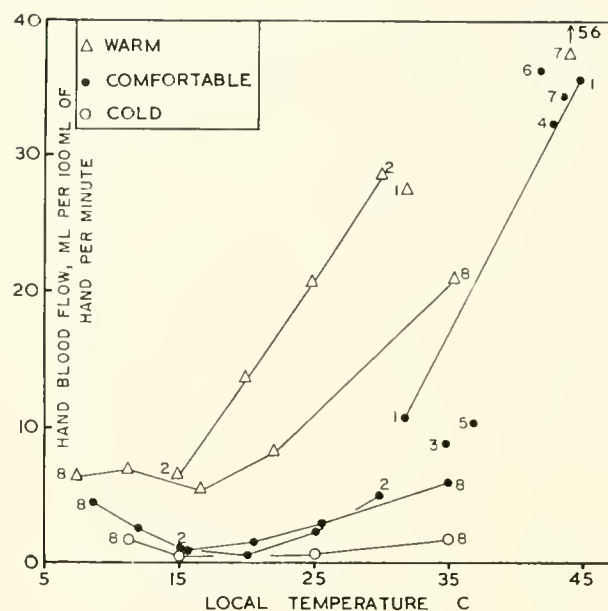


FIG. 2. The blood flow through the hand measured by venous occlusion plethysmography, in warm, comfortable, and cold subjects, and with the hand immersed in water at various local temperatures. [Data from: 1) Abramson *et al.* (4), 2) Catchpole & Jepson (47), 3) Killian & Oclassen (132), 4) Kunkel & Stead (136), 5) Kunkel *et al.* (137), 6) Peacock (159), 7) Roddie & Shepherd (166), 8) Speaman (180).]

partly by nervous reflexes and partly by alteration in temperature of the blood returning from the part to the heat-regulating center. However, the effects now to be described are predominantly local ones. When, for example, the temperature of the water around one finger or hand is altered, the changes in the circulation through it are very much greater than those simultaneously observed in the opposite member immersed in water at a constant temperature (55, 166).

LOCAL TEMPERATURES IN THE RANGE 15 C TO 45 C. Figure 2 summarizes some representative observations on the effect of immersion in water at temperatures in the range 15 C to 45 C on the rate of blood flow through the hand. Between the observations there are differences of age, sex, and number of subjects, of present and previous environmental temperature, in the length of exposure to the local temperature, and in the details of the venous occlusion plethysmographic technique. In general, however, it may be said that the blood flow through the hand is at its lowest value at about 15 C, when it may be as little as 0.3 ml per 100 ml of hand per min in a cold subject, and 0.9 ml in a warm one. From

15 C to 29 C there is a modest rise, and from 29 C to 35 C a faster rise in flow with temperature (180); 35 C to 37 C is the highest temperature to which the hand is normally warmed by the body's own heat. At local temperatures in the range 25 C to 35 C, the level of blood flow is greatly influenced by the heat-regulating mechanism of the body, and the observed values are distributed over a wide range. With further rise in local temperature from 35 C to 45 C, there is a steep increase in flow, to a maximum of about 35 ml per 100 ml per min (4); Peacock (159) found in 12 women an average of 36.0, and a range of 30.8 to 41.0; Kunkel & Stead (136) in 18 subjects at 43 C found an average of 32 and a range of 18.7 to 54.4. Even at high local temperatures the heat-regulating mechanism still exerts an influence, for if the subject is generally warmed the blood flow through the hand at 44 C increases to about 56 ml per 100 ml per min, individual observations of over 70 ml per 100 ml per min having been recorded (166). Most people find immersion in stirred water hotter than 45 C to be painful or intolerable.

In the foot, the effect of immersion in water at various temperatures is very similar to that in the hand, but the blood flow per unit volume of tissue is generally about 50 per cent, and per unit of surface area about 75 per cent (136), of that in the hand. Allwood & Burry (12) report average blood flows in four subjects ranging from 0.2 ml per 100 ml per min at 15 C to 16.5 ml at 44 C, and these seem typical. Thus in the range 43 C to 45 C flows have been reported of 14.8 in one subject (132); 16.3 with a range 11.1 to 20.9 in 33 male feet; and 18.7 with a range 13.4 to 25.9 in 15 female feet at 43 C, 90 per cent of the observations falling between 13 and 20 (136); 15.2 in one subject (4) and 20.5 in 33 subjects (191). The high blood flow with local heating probably has a useful protective effect. By conducting heat away from the tissues it reduces the temperature below the surface, and the likelihood of thermal damage. A hand immersed in stirred water at 45 C becomes painful if the circulation is arrested.

It takes time for the blood flow through an extremity to settle after a change of the temperature of the water in which it is immersed. Figure 3 shows blood flows after immersing the feet in water at various temperatures. The delay may be partly explained by the time needed for the internal tissues to reach a new equilibrium temperature. Once established the blood flow through the hand and fingers is well maintained after immersion for as long as 2 hours at 41 C (8).

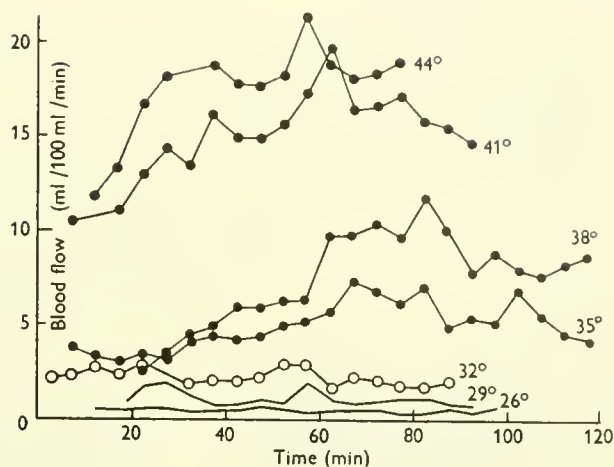


FIG. 3. Foot blood flow plotted against time of immersion during experiments at seven different temperatures. Each point represents the average blood flow over 5 min. [From Allwood & Burry (12).]

The local effect of temperature is usually very similar to normal in chronically sympathectomized hands (83), but an anomalous response has been reported in one case with a reduction in the blood flow through a sympathectomized hand on raising the temperature to 41 C (7). The response after chronic total denervation also appears to be similar to normal at local temperatures above 18 C (62). The vessels supposedly respond directly, but some recent evidence suggests that a local nervous pathway may assist. Irradiating the proximal half of the forearm with infrared rays causes a vasodilatation which spreads to the nonirradiated distal half; the spread is prevented by a cutaneous nerve block at the junction of the two halves of the forearm, and it is unaffected by sympathectomy, or by nerve block at the elbow (59).

LOCAL TEMPERATURE IN THE RANGE 0 C TO 15 C: COLD VASODILATATION. Lewis (140) observed that following exposure to low temperature the temperature of the skin rose above its former resting level. For example, following cooling for 15 min at 7 C, the temperature of the skin of the index finger rose to above 28 C, while that of the nonimmersed third finger remained at 19 C, the subject being in a room at 17.8 C to 19.1 C. The temperature of the index finger was at its maximum 11 min after cooling ended, and was raised for about 50 min.

Further observations showed that the vasodilatation started while the finger was exposed to cold. Figure 4 shows Lewis's experiment in which the R2

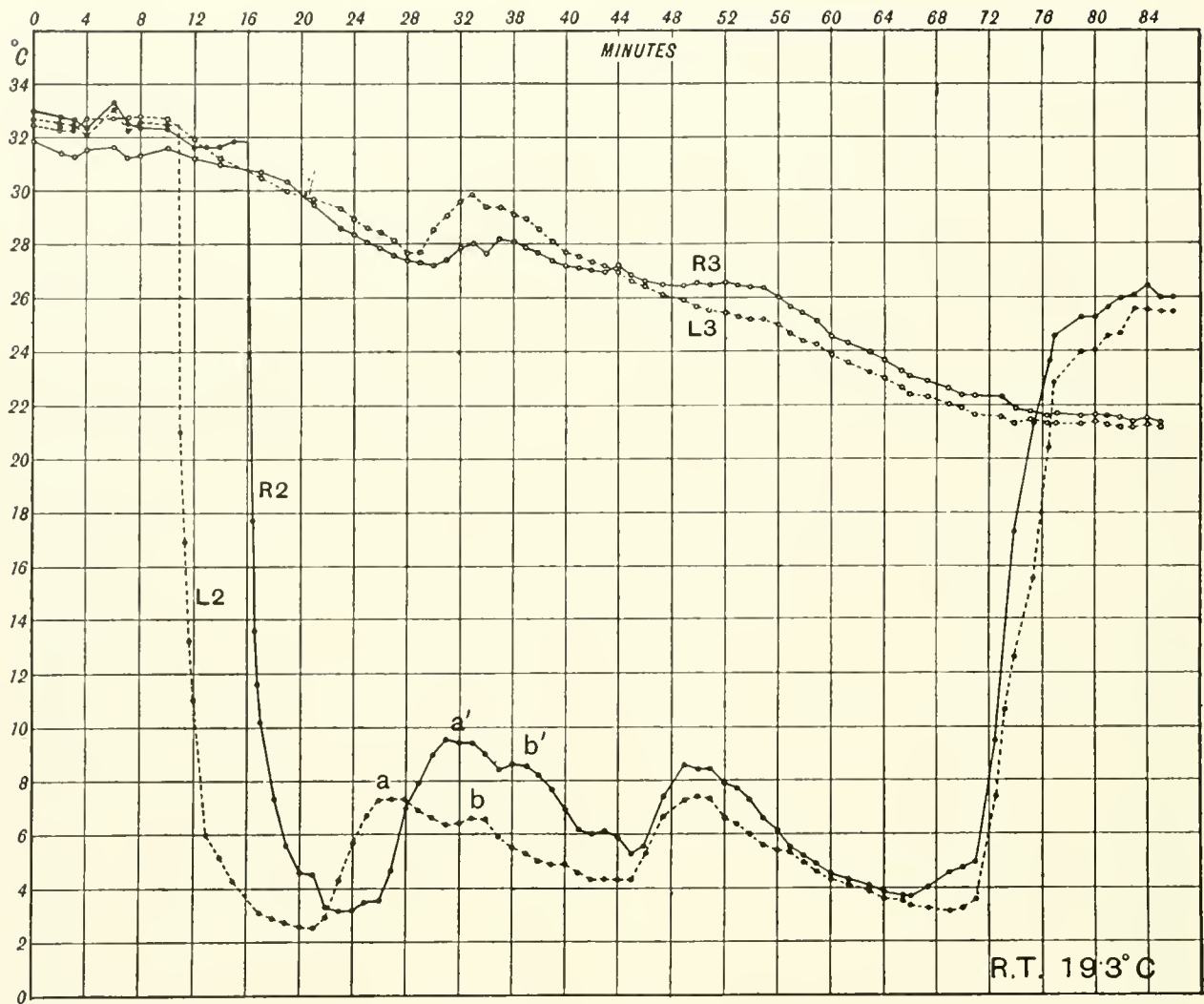


FIG. 4. Skin temperature measurements with a thermoelectric junction covered by adhesive plaster. Fingers *R3* and *L3* in air throughout. Finger *L2* in crushed ice from 11 to 71 min, finger *R2* from 16 to 71 min. The curves of temperature rise during immersion are in this case at first discordant, but become concordant. [From Lewis (140).]

and *L2* fingers were immersed in a mixture of crushed ice and water, the immersion of *R2* being delayed for 5 min. The *R3* and *L3* fingers remained in air and served as controls. The temperature of all digits was measured by thermoelectric junctions, covered by adhesive plaster; the thermal insulation of the plaster enabled the junction to assume a temperature different from that of the ice water with which it would otherwise have been in direct contact. On immersing the fingers, the temperature fell at first abruptly and then more slowly to about 3°C. About 10 min from the start the temperature of both immersed fingers began to rise. The rise was, in other experiments, prevented by arrest of the circulation

and it clearly indicated vasodilatation. The temperature thereafter fluctuated slowly (the so called "hunting reaction") and in the case shown the fluctuations in the two fingers became synchronous, although in other experiments initially synchronous fluctuations sometimes became discordant. Following removal from the ice water the immersed fingers became warmer than the control fingers.

A similar cold vasodilatation is strongly manifested in the toes, the lobe of the ear, and the tip of the nose; it is difficult to detect in the skin of the forearm, calf of the leg, and on the dorsum of the hand and foot (99, 140). Strong reactions are seen in the rabbit's ear (98) and in the foot of the domestic fowl and

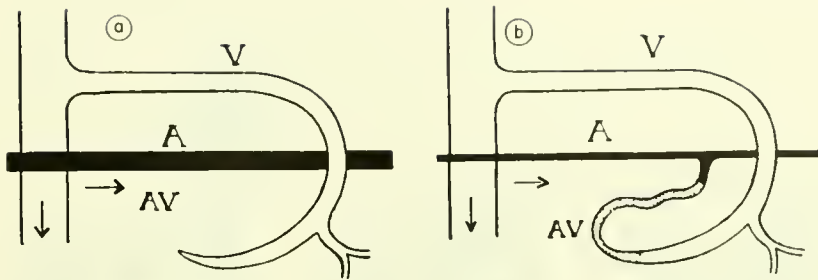


FIG. 5. Reaction of arteriovenous anastomoses in the rabbit's ear to local cooling, *a*, before and *b*, during cooling. A, artery; V, vein; AV, arteriovenous anastomosis, closed in *a* and open in *b*. [From Grant (98).]

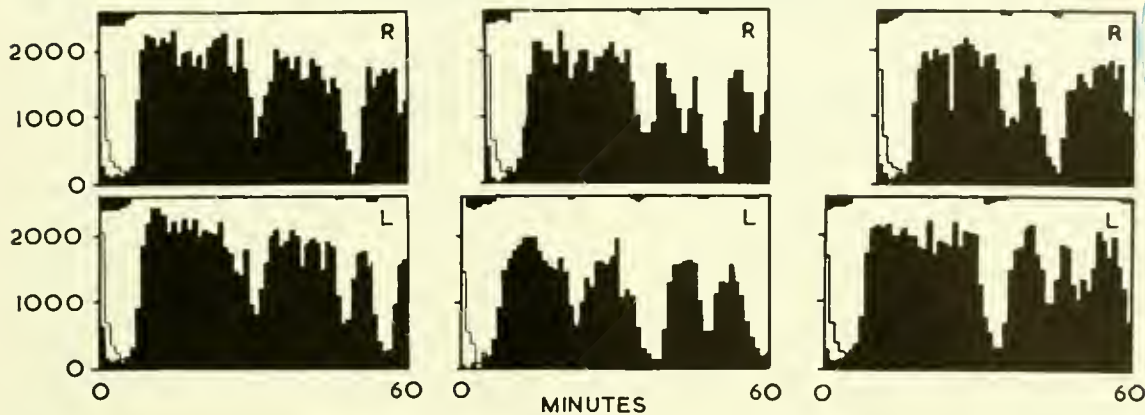


FIG. 6. The heat loss in cal/100 ml/min from the *R* and *L* index fingers to water in the range 0-6 C with intervals of 0 min (left), 5 min (middle), and 10 min (right) between their insertion into the calorimeters. The full width of the lower frames is 60 min. The clear areas represent heat derived from the tissues of the finger in cooling to calorimeter temperature during the first 6 min of insertion. Pain is represented on a roughly quantitative scale by marks at the top of the frames. The full height of the frame corresponds to a blood flow of not less (110) than 80 ml/100 ml of finger/min. [From Greenfield *et al.* (109).]

duck. The arteriovenous anastomoses in the rabbit's ear (fig. 5) were directly seen by Grant (98) to dilate to cold. In the hands and feet, and particularly in the digits, the intensity of the cold vasodilatation was found by Grant & Bland (99) to parallel closely the density of the arteriovenous anastomoses, and it seems likely that the dilatation of the latter is mainly responsible for the increased blood flow.

Subsequent calorimetric observations (16, 105) have shown that for the first 5 to 10 min of immersion in ice cold water there is a constriction of the vessels with almost complete arrest of blood flow (fig. 6). At this time there is a considerable degree of pain. The vessels then rapidly dilate, the pain goes and the finger feels warm and comfortable. In a warm subject, the blood flow may rise to a value which is probably as high as is attained by any other type of vasodilatation (105).

With continued immersion, the dilatation is irregularly interrupted by periods of constriction lasting a few minutes. These may be abrupt in onset

and termination, and may cause almost complete arrest of blood flow (108). The pattern and timing of these periods of constriction differ in different digits simultaneously observed, and appears to be locally determined (109). During continued immersion the general level of the peaks of vasodilatation often tends to decline, but if the subject is kept warm, alternation of dilatation and constriction may continue for several hours (37). On removal of a finger from the cold water the dilatation persists, and for about half an hour the finger may be warmer than its nonimmersed neighbors (192). The vasodilator response is conspicuous on immersion at temperatures near 0 C, but it is detectable at temperatures as high as 12 C or 15 C.

The vasodilator response is present after interruption of the sympathetic outflow from the central nervous system by local anesthetic block or by chronic section. It is, however, influenced by sympathetic activity. Among chilled individuals there are considerable differences in the response, but the vaso-



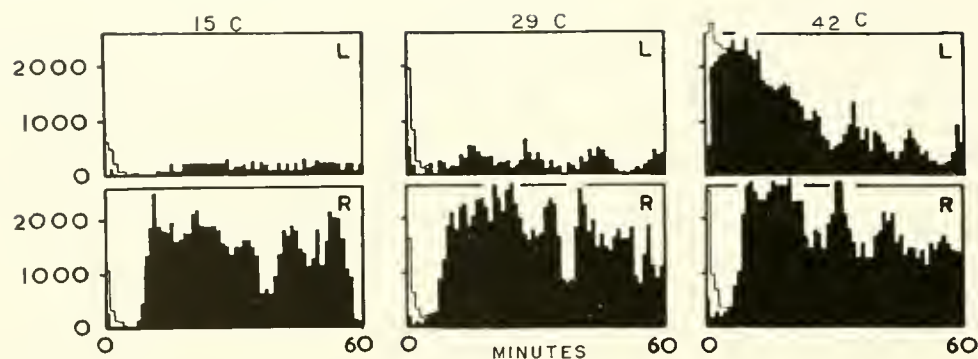


FIG. 7. Heat loss in cal/100 ml of finger/min to water in the range 0–6°C from the L (anesthetic) and R (normal) 5th fingers, the observations being made between the 30th and 40th days after division of the L ulnar nerve. In the denervated finger, cold vasodilatation is extremely small or absent after preliminary immersion in water at 15°C, small but definite after 29°C, and considerable after 42°C. [From Greenfield *et al.* (109).]

dilatation is delayed, sometimes for as much as 90 min from the time of immersion, and it is reduced in size sometimes to less than one-tenth (127). The response continues in the early days after interruption of the somatic nerves, but becomes difficult to elicit later when the separated distal parts of the nerves have degenerated. This led Lewis (140) to conclude that the response depends on a local axon reflex from cutaneous receptors to the blood vessels. If, however, the chronically denervated limb is warmed for some time before the digits are immersed in cold water (109), a reduced (to 20–90%) but definite vasodilator response is seen (fig. 7). It is always difficult to be certain that denervation is complete, but the observations probably indicate that the axon reflex pathway is not essential for the response. This view is strengthened by the finding of a vasodilator response in a finger tip locally injected with anesthetic solution (110). Other vascular responses which appear to be depressed in the chronically denervated limb are improved if the limb is first warmed for an hour or two.

A chemical stimulus to cold vasodilatation has not been identified. Acetylcholine and histamine injected intra-arterially or introduced by electrophoresis during the first few minutes of immersion of a finger in ice water do not provoke an earlier vasodilatation, but it is possible that at this time of intense vasoconstriction they do not reach the blood vessels. Cold vasodilatation, however, is not reduced by atropine nor by antihistamine (188). The mechanism of the response remains obscure.

The effect of the dilatation is to raise the temperature of the exposed extremities at the expense of a considerable loss of heat from the body. Even while

immersed in stirred water near the freezing point, the average internal temperature of a finger may be raised to as much as 30°C, and in the central parts must presumably be only slightly below the temperature of the body core (107). In a warm person the heat loss per minute from a whole hand and from the distal half of a foot may be 800 and 407 cal per min, respectively (104). These figures are similar to total resting heat production, and the loss of heat from one hand can cause a fall in esophageal temperature of 0.6°C in 9 min (106). When plenty of heat is available, the reaction keeps fingers exposed to reasonable cold sufficiently warm to preserve movement and sensation. Dwellers in cold climates normally wear clothing which provides their body with a warm microclimate, and are able to afford some heat loss. When there is a need to conserve heat, the reaction is greatly diminished and the fingers are only slightly warmed by it. For example, Australian aborigines are able, by restricting the peripheral circulation, to retain sufficient heat to sleep naked through the night in a temperature which may fall to 0°C (177).

Several observations suggest that the extremities can become acclimatized to cold (44). Local pain, and the reflex increases in arterial pressure and pulse rate are reduced after repeated immersion in water at 4°C (92). Exposure of the fingers to severe cold causes less numbness in persons habitually exposed than in others. Such observations suggest that there may be a local adaptation of the circulation in the exposed parts but the evidence for this is not strong. Repeated exposure of the hands to cold, as in Norwegian and Lapp fishermen, leads to a more rapid onset of cold vasodilatation (135) but to no increase

in the level of blood flow at the height of the vasodilatation (113, 135). In such subjects, kept warm to release sympathetic vasoconstrictor tone, the reactive hyperemic blood flow with the hands at 40 C, and the resting blood flow with the hands at 40 C, 20 C, and 10 C is no different from that in normal controls (135). The improved circulation in the hands of cold-habituated persons reported by other observers may depend more on general adaptation of the circulation than on a local adaptation in the periphery.

PROLONGED EXPOSURE TO COLD: TRENCH FOOT AND IMMERSION FOOT. Prolonged local cooling to temperatures above the freezing point is capable of causing serious injury. Although in many recorded cases the parts have been wet as well as cold, the main factor is the cooling of the extremities in a chilled subject (183). The feet are particularly liable to injury, and most cases have been seen after exposure for many hours or days in war time.

The four stages of the condition have been well described by Ungley (183).

1) During exposure, the limb is numb, power is reduced, and movement is clumsy. Pain is unusual. Swelling is common, the limb often looks bright red, and there may be periods of warmth, presumably due to cold vasodilatation, but the chilling of the subject reduces this to small proportions.

2) Immediately after rescue and return to warmth and shelter there is a prehyperemic stage, which may last for 2 to 5 hours. The limb is cold and either pale with cyanotic patches or cyanosed. The arterial pulsations cannot be felt. There is a partial or complete "stocking" sensory loss.

3) A hyperemic stage follows, the part becoming red, swollen, painful, and sometimes blistered. When the arterial pulses return, they are very strong, and the temperature of the skin is as high as that of the axilla or groin. The hyperemia is judged clinically to be at least as great as that following sympathectomy, and it is often much more persistent, lasting as long as 14 weeks. There is partial anesthesia, and vasomotor and sudomotor paralysis, indicating nerve damage. In addition there is direct vascular damage.

4) In mild cases there is a return from the hyperemic state to normal, but in severe cases a post-hyperemic state follows. The circulation decreases greatly, and although vasomotor reflexes to heating and cooling the rest of the body return, the response is slow and incomplete. There is often an increased sensitivity to cold, reduction of the blood flow for many hours sometimes following immersion in water

at a temperature as high as 24 C. Once constricted or dilated, the vessels tend to remain so for a long time. The cause of this altered vascular reactivity is not known.

Although the vascular damage may not be an essential feature (183) it may sometimes be severe (84) with dilatation and engorgement of vessels, rupture, and thrombus formation. Exposure for many days to water at as high a temperature as 21 C has been sufficient to cause the feet to become swollen, hyperemic, and painful (186). Of nine volunteers living for 5 days in a covered raft in arctic waters, seven developed hyperemic swollen feet, a condition which in two cases persisted for several weeks; the lowest toe temperature recorded during exposure was 11 C, and the temperatures were usually 13 C to 15 C. (44). The vascular changes during exposure have not been followed in man. It is presumed that cold vasodilatation subsides after a time, perhaps because the subject becomes generally chilled, and that there is an extremely low blood flow for a long time.

EXPOSURE TO SEVERE COLD. FROSTBITE. Exposure to a temperature sufficiently low to cause freezing of the tissues may cause frostbite, which is commonly followed by gangrene and loss of tissues. During exposure there is arterial spasm and capillary stasis. On rewarming, there is an intense hyperemia, and the capillary permeability is greatly increased, leading to edema and to blockage of the vessels with blood cells. There is frequently thrombosis in some vessels and this may lead to a permanent reduction in blood flow (149).

The freezing point of living fingers is about -0.6°C , but supercooling is usual so that fingers immersed in brine at -1.9°C , the freezing point of sea water, do not always freeze (128). Supercooling to -1.9°C does not cause the tenderness, redness, and warmth which persist for several days after freezing at that temperature. The damage on freezing the tissues is probably caused partly by the formation of ice crystals, and partly by the concentration of the dissolved substances in the liquid water that remains (150).

In dogs, after immersion of the hind leg in an alcohol and dry ice mixture at -25°C for 30 min, or -4°C to -8°C for 210 min, the blood flow, on rewarming the limb, is increased for several hours to several times the level in the contralateral control limb (125) and this vasodilatation appears to depend on the integrity of sympathetic outflow (126).

Reactions to Injury

MECHANICAL INJURY. The reactions to mechanical injury were very completely studied by Lewis (139).

The white reaction. When warm skin is lightly stroked with a blunt point there is a temporary blanching as blood is expressed from and then returns to the superficial vessels. About 15 sec later, the line of the stroke becomes pale again, the pallor reaching its maximum about 30 sec after the stroke, and fading in about 3 to 5 min. The white line is sharply localized to the area stroked. Its development is unaffected by the temporary arrest of the circulation, and it was therefore taken by Lewis to indicate active contraction of the vessels responsible for the color of the skin, and not merely deprivation of these vessels by contraction of the arterioles that supply them. The vessels responsible for color are able to sustain their contraction against a distending pressure of 80 to 100 mm Hg produced by venous congestion.

The triple response. When the stroke is much or very much firmer, the white reaction is replaced by a different response which, when fully developed, has three components, the red line, flare, and wheal. *a)* The most constant component is a sharply demarcated red line which develops along the line of the stroke with a latency of 3 to 15 sec, and the intensity and duration of which increase with the strength of the stimulus. Like the white reaction, the red line develops even when the circulation is temporarily arrested. It was considered by Lewis (139) to indicate active dilatation of the vessels responsible for the color of the skin. *b)* In susceptible skins, and with strong or repeated stimuli, an irregular red flare develops about 15 to 30 sec after the red line, and gradually extends for 2 to 3 cm on each side of the line of the stroke. The flare remains a bright scarlet color, unlike the red line which becomes progressively dusky. As the flare fades, it becomes mottled. A white reaction can be developed across the flare by light stroking, but not across the red line. The flare was considered by Lewis (139) to indicate arteriolar dilatation. *c)* In sensitive skins, or in others following a strong stimulus such as the lash of a whip, a raised wheal usually begins to appear along the line of stroke in 1 to 3 min, reaching full development in 3 to 5 min. It overlies the red line and the line becomes pale, presumably because of the pressure exerted by the transuding fluid upon the minute vessels.

The triple response is unaffected when the sensory nerves are freshly interrupted by section or local

anesthesia. The red line and the wheal continue in chronically denervated skin, but the flare is lost after about the sixth or seventh day when the sensory nerves degenerate. This led Lewis (139) to conclude that the red line and wheal are independent of nerves, but that the flare depends on a local axon reflex (49). The nerve impulse arises in a receptor in the skin and, after ascending a sensory nerve for some distance, returns antidromically along a branch to arrive at an arteriole and cause it to dilate.

The triple response is the standard reaction of the skin to a great variety of injurious stimuli. The response to mechanical trauma can be exactly reproduced by pricking histamine into the skin. Further, if trauma or a histamine prick is applied while the circulation is arrested the development of the flare is delayed until the circulation is released. This and other evidence led Lewis (139) to postulate that the flare depends on the activation of the skin receptors by an H-substance, which may be histamine, rather than directly by the mechanical trauma.

ULTRAVIOLET LIGHT. Irradiation with ultraviolet light, which penetrates to a very small depth in the

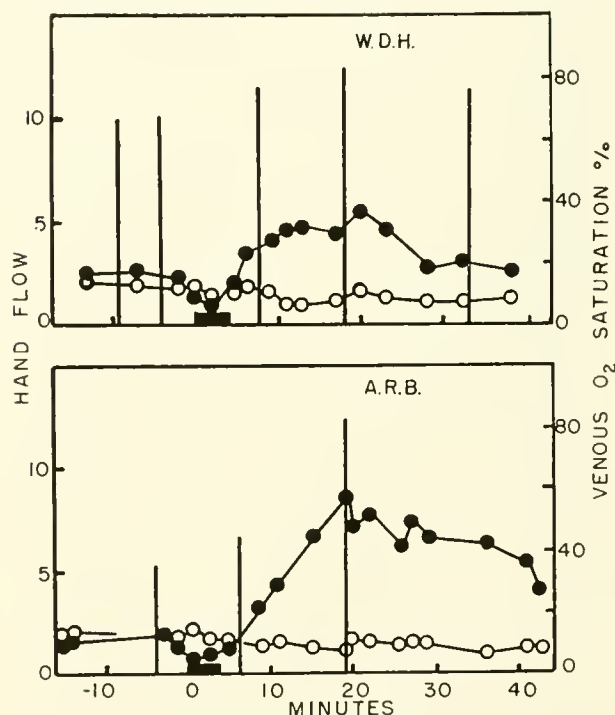


FIG. 8. Two experiments. Hand blood flow in ml/100 ml/min. Solid circles: injected arm; open circles: control arm. The heights of the vertical columns indicate the percentage saturation of venous blood with oxygen. Intra-arterial injection of 5 ml of nitrous oxide is indicated by the black rectangle starting at 0 min. [From Duff *et al.* (67).]

skin, causes a delayed erythema sharply confined to the exposed area. It is probable that a chemical agent is concerned, but that this is not histamine (156).

ARTERIAL GAS EMBOLISM. After injection into the brachial artery of 1 to 10 ml of gas there is usually an immediate reduction in blood flow through the hand lasting for a few minutes, followed by a prolonged increase, to several times the normal resting rate, which does not entirely subside for many hours (66). The increase in the oxygen saturation of the venous blood parallels the increase in flow (fig. 8). All of the several gases tested are effective, provided they are given as bubbles and not in solution. The response is present in both sympathectomized and chronically denervated limbs, and is unaltered in the presence of amounts of antihistamine substances which prevent the action of histamine (67). The vessels of muscle as well as of skin are affected. The mechanism is not understood, but the reaction appears to result from some trauma to the tissues caused by the bubbles, and a peripheral arterial conducting mechanism may be involved (120).

NERVOUS CONTROL OF SKIN BLOOD VESSELS

Vasomotor Nerves

VASOCONSTRICTOR SYMPATHETIC NERVES. Claude Bernard (30, 31) showed that division of the cervical sympathetic chain in the rabbit caused the ear on the same side to become flushed and warm. Stimulation of the trunk had the reverse effect (32). Similar observations were made by Brown-Séquard (39). These observations indicate that the sympathetic nerves contain vasoconstrictor fibers, and that under ordinary conditions the activity in these fibers keeps the vessels in a partially constricted state. The warming of, and increased circulation through, the human feet and hands following lumbar and thoracic sympathectomy was first described by Adson & Brown (5, 6) and this established that these areas were similarly under sympathetic vasoconstrictor control. Walker *et al.* (184) made quantitative measurements of the effects of sympathectomy in patients with apparently normal blood vessels in whom the operation had been carried out as a treatment for excessive sweating. The blood flow in milliliters per 100 ml of hand per min was increased from an average value

of 5.2 before the operation to peak values in the range 22.7 to 59.2 after the operation, and in the feet was increased from an average value of 2.1 before the operation to peak values in the range 20.8 to 28.0 after the operation. The averaged results on five hands and six feet are shown in figure 9.

In vasoconstrictor sympathetic nerves low rates of discharge have a powerful effect; in the cat's paw, stimulation at the rate of 1 per sec increases the resistance to flow about 10 times, and stimulation at 10 per sec increases it about 100 times (48).

VASODILATOR SYMPATHETIC NERVES. The evidence for vasodilator nerves to the skin rests at present on experiments of the type employed by Grant & Holling (100), that is to say, on the simultaneous observation under suitable conditions of reflex stimulation of a greater blood flow in normally innervated skin than in a corresponding area of skin acutely deprived of its vasomotor innervation. Since both areas are perfused with blood of identical composition and at the same pressure, the resistance vessels may be presumed to be more widely dilated in the innervated skin, and this dilatation to result from nervous activity. It must be noted that chronically denervated skin is not a satisfactory tissue for this comparison, because of the decline in blood flow due to contraction of the blood vessels.

Grant & Holling (100) found that blocking the cutaneous nerves, which convey sympathetic fibers, to parts of the skin of the forearm not only failed to cause a flushing and rise of temperature but prevented the vasodilatation and also the sweating normally seen in the forearm during body warming. Evidently, in the forearm vasomotor nerves actively bring about vasodilatation. Whether they do so by a direct action on the vessels or as a consequence of increased sweat gland activity, or by both means was, and is, uncertain. If the fibers are called "vasodilator," it must be remembered that vasodilatation may be only a consequential and not a direct effect.

It is, of course, important for heat to be brought to the skin if sweat is to be evaporated. At least 60 ml of blood are required to transport from the body core the heat required to evaporate 1 g of sweat when the skin is 10° below the temperature of the core. At least 600 ml of blood are required when the skin is 1 C below the temperature of the core. Sweating can therefore be effective only when accompanied by vasodilatation.

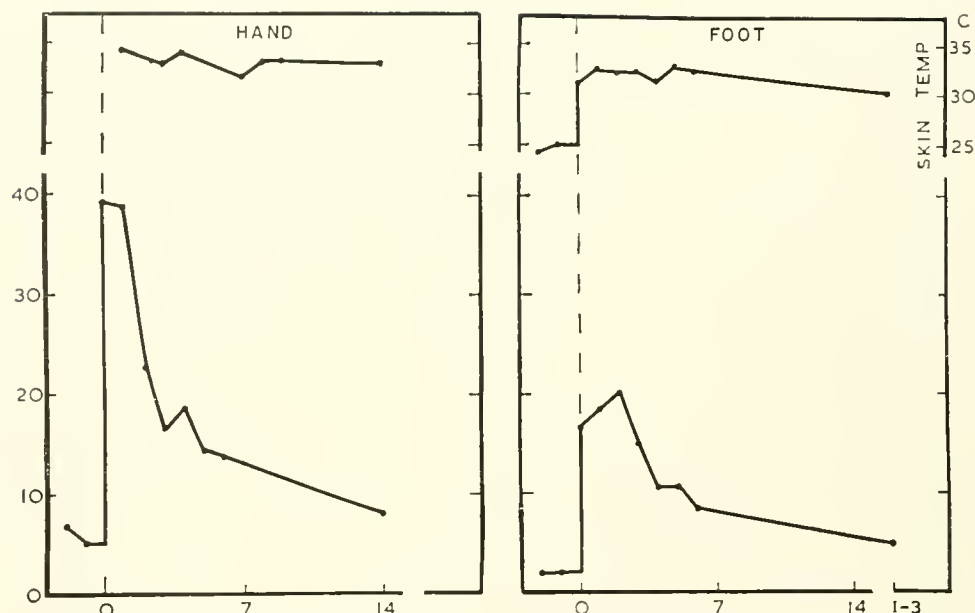


FIG. 9. *Abscissae*: time in days, the vertical broken line indicating the day on which sympathectomy was performed. *Ordinates*: blood flow in ml/100 ml tissue/min. The averaged results of experiments on five hands and six feet show the effect of sympathectomy on the blood flow in the hand and foot, and on the skin temperatures of the fingers and toes. The denervations were performed to prevent excessive sweating; hence the responses are those of normal human blood vessels. Note the transient increase in blood flow after operation and the subsequent decline as intrinsic tone returns to the vessels. [From Barcroft (18).]

VASODILATATION CAUSED BY ANTIDROMIC STIMULATION OF DORSAL ROOT SENSORY NERVES: THE AXON REFLEX PATHWAY. Stimulation of the peripheral end of a cut sensory nerve often causes vasodilatation in the area of skin supplied by the nerve, and Bayliss (24) showed that this was due to impulses traveling toward the periphery along neurons of the dorsal root system. The vasodilator effect of such antidromic nervous impulses is considerable, but evidence has not been forthcoming for the use of this route from the central nervous system to the periphery for any reflex adjustments of the circulation. It seems probable that the artificially provoked antidromic impulses travel to the vascular nerve endings of the peripheral axon reflex pathway. The usual source of impulses arriving here is from nearby sensory nerve endings, probably subserving pain sensation. The transmitter substance for the vasodilatation produced in the chronically sympathectomized ear of the rabbit by stimulation of the sensory great auricular nerve is neither histamine nor acetylcholine (123) but is probably adenosine triphosphate (122), the presence of which has been demonstrated in nerve roots (121).

Innervation of the Blood Vessels of the Skin in Different Areas

The problem is to define, for different areas of skin, the existence and range of action of vasoconstrictor and vasodilator fibers. This has been most fully investigated in the human limbs, particularly in the upper limbs, and the innervation here will be first described.

THE HUMAN HAND AND FINGERS. In the cold subject, the blood flow through the hand is very small, often less than 1 ml per 100 ml per min. When the subject is warmed, either in a hot cabinet (143) or by immersing the legs in stirred water at 44°C (89), the blood flow increases to about 30 ml per 100 ml per min, this being part of the general response by which the body attempts to lose heat. Although abundant cholinesterase is found in the arteriovenous anastomoses of the fingers, and although Lewis & Pickering (143) obtained evidence in cases of Raynaud's disease for the activity of vasodilator nerves, the increase in blood flow in normal persons can be entirely accounted for by a reduction in the activity of vasoconstrictor nerves; several careful investigations have

failed to detect any contributions from vasodilator nerves. Thus Pickering (161) during body heating found equal rates of heat elimination from the two hands, the ulnar nerve conveying part of the sympathetic supply to one hand having been blocked. In a more sensitive test, Arnott & Macfie (15) measured the heat elimination from the fifth fingers during body heating. The sympathetic supply to one was entirely interrupted by ulnar nerve block, but the rates of heat elimination were equal. Warren *et al.* (185) found that paravertebral block of the sympathetic outflow increased rather than decreased the blood flow through the hand of a heated subject. Gaskell (87) compared the rates of blood flow through the two hands by venous occlusion plethysmography, which is probably the most accurate method. He heated the subject, and then blocked on one side near the elbow the radial, ulnar, and median nerves which probably convey the great majority of sympathetic fibers to the hand. This caused no alteration in the rate of blood flow. Roddie *et al.* (172) found no difference between the rates of blood flow through the two hands in similar experiments in which the nerve block on one side preceded the body heating; this eliminated the possibility that in Gaskell's experiments (87) a stable chemical vasodilator substance was released by sympathetic nerves before they were blocked. The most probable explanation of these observations is that in the adequately heated subject there is a complete cessation of activity in the vasoconstrictor nerves to the hand, and no activity in vasodilator nerves. The less probable alternative is that in the hand of a heated subject there is a balance of vasoconstrictor and vasodilator activity, and that the vessels are unaffected when both activities are abolished by nerve block.

Although there is no evidence for the participation of vasodilator nerves in the response to body heating in normal persons, a vasodilatation dependent on an intact sympathetic nerve supply may accompany the sweating in the hand which is provoked by emotional stress. The direct and immediate effect of emotion is to reduce the blood flow through the hand (2) by increasing the activity in vasoconstrictor nerves. If, however, the emotional stress is continued, as by mental arithmetic, the vasodilatation consequent on sweating may outweigh the constriction even in normal persons, and in persons suffering from excessive sweating the vasodilatation may be very large indeed (10), the flow rising from 5 to over 30 ml per 100 ml per min (fig. 10).

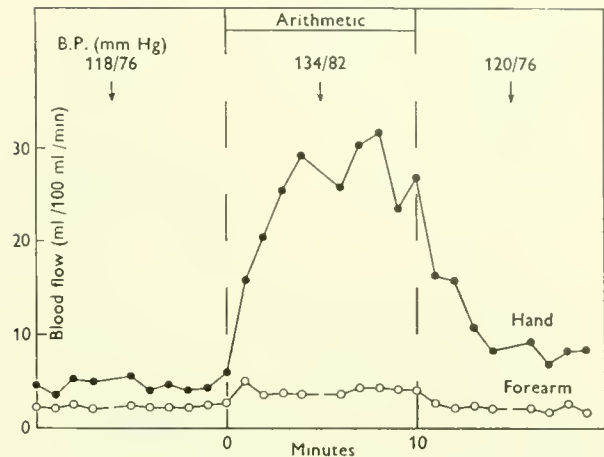


FIG. 10. Results showing the marked increase in hand blood flow (●) during mental arithmetic in a hyperhidrotic subject. There was little change in the forearm blood flow (○) or arterial blood pressure. Plethysmograph temperature 36 C. [From Allwood *et al.* (10).]

THE HUMAN FOREARM. Both vasoconstrictor nerves, and nerves which directly or indirectly cause vasodilatation (vasodilator nerves) regulate the circulation through the skin of the forearm. Of these, the vasodilator nerves, first described by Grant & Holling (100), are by far the more important. The role of the two sets of nerves is clearly displayed during the response of total forearm blood flow to general body heating.

This response has recently been shown, by several methods, to be confined to the skin, the muscle circulation remaining unchanged. Thus Edholm *et al.* (71) found that intensive iontophoresis of adrenaline, sufficient to arrest the circulation in the skin of the forearm, prevented the normal increase in total forearm blood flow with body heating. Barcroft *et al.* (20) found that when a person is heated the total blood flow through the calf of the leg, measured plethysmographically, increases, but that through the muscle, measured by a heated thermocouple method, does not; the increase must have been in the skin. The rate of clearance of radioactive sodium from muscle is unchanged or reduced (154). Roddie *et al.* (170) found that during general body heating there was a gradual increase, from an initial 40 to 72 per cent to a final 85 to 99 per cent, in the oxygen saturation of the blood in the superficial veins of the forearm predominantly draining skin, but no change in the deep veins mainly draining muscle (fig. 11); the changes in the superficial blood closely paralleled the increase in total forearm blood flow in the opposite arm.

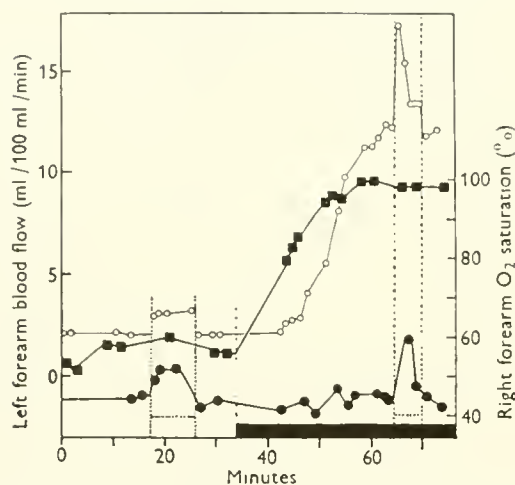


FIG. 11. The effect of body heating and of change of posture on the oxygen saturation of deep and superficial forearm venous blood. The black rectangle indicates the period of general body heating. The intervals between the dotted lines represent the periods during which the subject's legs were passively raised. ○, Left forearm blood flow; ■, oxygen saturation of superficial venous blood in right forearm; ●, oxygen saturation of deep venous blood in right forearm. [From Roddie *et al.* (170).]

On warming a rather cold subject, the blood flow through the forearm, and hence through the skin of the forearm, increases in two steps (171). The first increase, from about 2 to about 4 ml per 100 ml per min, is of the same order of size as the increase which follows block of the superficial nerves to the forearm, and may be assumed to be due to withdrawal of vasoconstrictor activity. The subject is by now comfortably warm. If body heating is continued, there is a further increase in forearm flow from 4 to 10 to 15 ml per 100 ml per min. This is accompanied by sweating. The total forearm blood flow and the oxygen saturation of the blood from superficial veins now far exceed the levels seen after cutaneous nerve block. Blocking the cutaneous nerves at this stage causes the forearm blood flow to fall to about the level seen in an unheated subject (72). Without block, the blood flow through the skin of the forearm is now very large indeed; Edholm *et al.* (71) give a figure of 165 ml per 100 ml of forearm skin per min, but do not claim that this is more than an approximate figure. The sweating can be prevented and the vasodilatation delayed by the injection of atropine into the brachial artery before the heating starts. Fox & Hilton (81) have found that during sweating there is a fivefold increase in the bradykinin-like activity in the perfusate of the subcutaneous tissue of the forearm, and that a bradykinin-forming enzyme is present in sweat. Bradykinin is a very powerful vasodilator

substance. Injected into the human brachial artery it is more powerful, per molecule, than acetylcholine or histamine, or indeed any other known substance (80). It is suggested (81) that the vasodilatation in the skin of the human forearm is produced in the main by bradykinin resulting from sweat gland activity, itself provoked by cholinergic sympathetic nerves.

In the region of the wrist there must be a transition from the vasoconstrictor control of the hand vessels to the predominantly vasodilator control of the forearm vessels. The site, sharpness, and variability or constancy of the demarcation have not been defined.

OTHER AREAS OF THE HUMAN BODY. The innervation of the foot has been less completely examined than that of the hand, but as far as is known, the pattern is similar. Elsewhere, our knowledge is fragmentary and incomplete. In the upper arm, calf of leg, and thigh (36) the pattern of vasomotor innervation is like that of the forearm, there being a weak vasoconstrictor innervation operating when the subject is cold, and a more powerful vasodilator innervation, probably associated with sweat gland control, which operates when the subject is hot. Vasodilator control is also dominant in the forehead and chin, and cutaneous vasodilatation accompanies sweating in these areas; vasoconstrictor control is important in the glabrous portion of the lips, and in the skin of the nose (78, 79).

THE SKIN OF ANIMALS. Apart from the paws (138), the skin of the limbs of cats and dogs lacks eccrine sweat glands. In these species, heat vasodilatation results from the reduction in the activity of vasoconstrictor nerves, and there is no evidence for vasodilator nerves (77, 102).

LATE EFFECTS OF SYMPATHETIC DENERVATION. Goltz & Freusberg (97) noted that the freshly denervated leg of the dog was warmer than its fellow, but that the difference does not persist. It has since been shown by several groups of workers (18, 23, 101, 145, 184, 190) that the blood flow in a limb several weeks after sympathectomy differs little from the preoperative value. The blood flow in both hands and feet reaches its highest value about the second day after the operation, and then declines steeply during the next few days (fig. 9). In the hand, the decline in flow is equally rapid whether a preganglionic section or a postganglionic section with ganglionectomy has been performed (184). In the forearm (63) the maximum

flow is seen on the day of the operation, and the decline is faster than in the hand; the extent to which the vessels of muscle and skin, respectively, contribute to these changes has not been defined.

The cause of the change in the vessels which leads to the return of blood flow to near the normal level is not known. The denervated vessels develop an increased sensitivity to adrenaline and other vasoactive agents (46, 74) and this develops at a rate which closely parallels the decline in blood flow (22). Increased sensitivity of chronically sympathectomized vessels has been demonstrated in the finger to adrenaline injected intravenously (178), and in the hand to both adrenaline and noradrenaline injected intra-arterially (fig. 14). Whether the return of tone is due to an increased sensitivity of the vessels to unknown circulating pressor substances, or to an intrinsic change in the muscle of the vessel wall, or to an effect of surviving accessory sympathetic fibers is not decided.

LATE EFFECTS OF TOTAL DENERVATION. "While loss of sympathetic supply causes the corresponding fingers to be in general warmer than they otherwise would be, loss of all nerve supply causes the corresponding fingers to be in general colder than they otherwise would be. And, since with combined loss of both motor and sympathetic supply the digits remain warm, it seems that sensory nerve loss must be an important factor in determining the persistent coldness in cases of mixed nerve lesions" (Lewis & Pickering, 144). The extent to which the coldness of denervated fingers depends on the loss of sensory as opposed to sympathetic innervation has, however, been questioned (62), and limbs normal except for muscular paralysis are colder than normal (144). The most conspicuous abnormality in the behavior of the circulation in denervated digits is the great reduction, under normal circumstances, in the vasodilator response to cold.

Reflex Control of Blood Vessels of the Skin

The blood flow through the digits can be varied through a very wide range by the activity of the sympathetic vasoconstrictor nerves. At the upper and lower extremes of the range the blood flow is normally fairly steady from minute to minute. At intermediate levels, such as are normally found in comfortably warm subjects, the flow usually fluctuates, rising and falling by 20 per cent or more several times a minute. The fluctuations are abolished by division of the

sympathetic nerves, occur simultaneously in the digits of all limbs, and are often associated with simultaneous changes in heart rate (41, 42, 45). The frequency of the constrictions is greater when the flow is near the lower than when it is near the upper end of its range, and the size and pattern of the variations vary considerably in different individuals. The functional significance of the fluctuations is not known; their occurrence makes desirable the use of repeated rather than single observations in estimates of the skin circulation in the extremities. They are not found in the skin of the forehead (117).

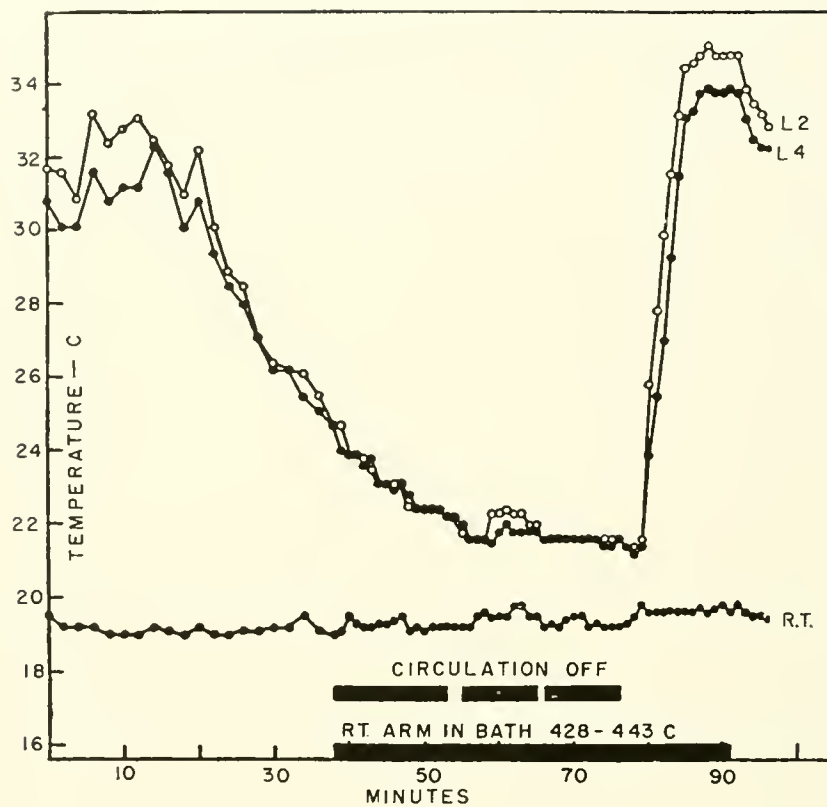
Very little is known about the reflex responses of skin other than that in the extremities, but such evidence as is available indicates that the responses, if present, are comparatively small (85, 116).

BODY TEMPERATURE REGULATION. The skin is a main route for loss of heat from the body, and by far the most important route capable of adjustment by the temperature-regulating center. The heat lost from the surface, whether by conduction, convection, radiation, or the evaporation of sweat must be transported to the skin, and because of the low thermal conductivity of body tissue, the transport is mainly in the circulating blood.

Gibbon & Landis (89) found that if one arm was immersed in water at 42.5 C to 44.6 C the temperature of the fingers of the opposite hand started to rise in 5 to 10 min, and reached 32 C in 9 to 16 min. If, however, (fig. 12) under similar conditions, the circulation in the immersed arm was arrested (with brief releases) by a pneumatic cuff for the first 35 min of immersion, the rise in temperature of the fingers of the opposite hand was delayed until 7 to 10 min after the final release of the cuff (that is 42-45 min from the start of immersion), and the fingers reached 32 C 11 to 16 min after the release. The response in the fingers evidently depends on the return to the body of hot blood from the immersed part, rather than on the stimulation of peripheral receptor organs. This conclusion is confirmed by the finding that rapid intravenous infusions of hot saline are able to provoke vasodilatation in the hand by a mechanism independent of any surface heating (179). The central receptor mechanism is sensitive to the addition of as little as 1 to 2 Calories of heat to the body, or to an amount of heating sufficient to raise the sublingual temperature by 0.15 C (88).

The temperature of surface receptors is, however, of some importance in the reflex regulation of the skin circulation. Kerslake & Cooper (129) found that

FIG. 12. The right arm, with the circulation off, was immersed in hot water at 42.8–44.3 C at the 38th min. There was no dilatation in the left second (L_2) or left fourth (L_4) finger until the circulation was released at the 76th min. [From Gibbon & Landis (89).]



heating the trunk or both legs with radiant heat caused a substantial (2-fold or 3-fold) increase in blood flow through the hand, with a latency of only 10 to 15 sec; this was too short a time for a mechanism depending on the return of hot blood to the heat-regulating center. Furthermore, on heating the legs the response was unaffected when cuffs around the thighs were inflated to 200 mm Hg to arrest the circulation (fig. 13). In this case the vasodilatation therefore appears to depend on afferent information conveyed by nerves from the heated skin. The response to heating the legs disappears after bilateral lumbar sympathectomy, and in persons with unilateral sympathectomy it is obtained on heating the normal but not the sympathectomized leg (57). It is not yet certain whether the afferent nerves traverse the sympathetic ganglia, or whether sympathectomy modifies the response by altering the conditions at somatic nerve thermoreceptors. Stimulating the intact lumbar sympathetic chain or its cut central end causes vasoconstriction in the hand, but it is not known whether the stimulated afferent fibers are from the skin or from the viscera (58).

As mentioned earlier, the effector side of the temperature regulation reflex is mediated in the hand by adjusting vasoconstrictor activity, and in the forearm

mainly by adjusting vasodilator activity. The reduction in vasoconstrictor activity is not simultaneous in all areas; the individual fingers often dilate asynchronously, and the foot often dilates many minutes after and less completely than the hand (162). The vessels in warm skin dilate sooner than those in corresponding areas of cold skin.

Exposure of part of the body to cold causes changes in the circulation in other areas by two mechanisms. There is a rapid transient reflex vasoconstriction, due to stimulation of afferent nerves (160), and a longer lasting vasoconstriction due to cooled blood returning to the heat-regulating center (160, 181). The cooling effect on the temperature of the body core of exposure of limbs to cold is usually restricted by local vasoconstriction. This limits the quantity of cooled blood returning to the core. Furthermore the efficient arrangements for exchange of heat between arteries and veins in the limbs (25, 26) reduce the cooling effect of the blood. On the other hand, the temperature of the blood that does return may, at the start of its journey, be 30 C or more below that of the core, while from a heated region the blood can hardly start its return at a temperature more than 7 to 8° above that of the core. Further, cold may sometimes be sufficiently severe to cause cold vasodilatation,

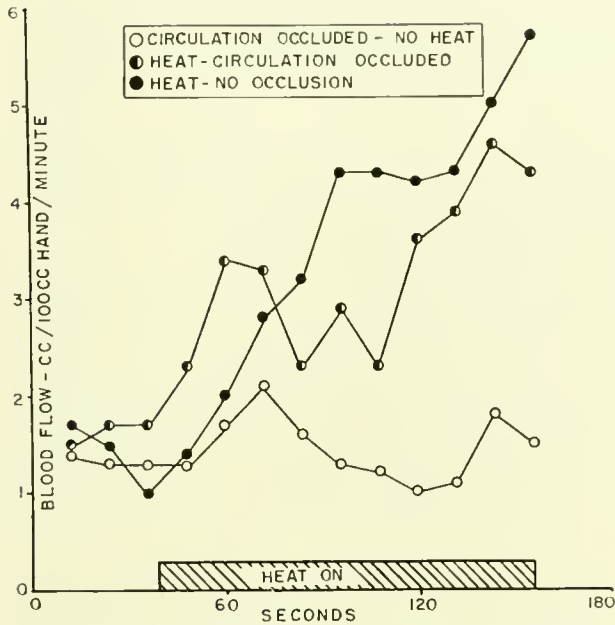


FIG. 13. Changes in hand blood flow during heating of the front of the legs. Each curve is the mean of three runs. [From Kerslake & Cooper (129).]

and while this is in progress the heat loss may be several times greater than the heat gain during exposure to heat.

When a nude person is chilled, the temperature of the skin and the loss of heat from it fall to much lower levels over the limbs, and particularly the hands and feet, than they do over the head, neck, and trunk. This difference is partly accounted for by the more vigorous vasoconstriction in the skin of the limbs, and partly by the more favorable opportunities in the limbs for economizing heat loss by exchange of heat between arteries and veins. Thus there are poor defenses against heat loss from the head and trunk, and these regions are particularly dependent on clothing for insulation. The loss of heat from the uncovered head may be very large (85), amounting to about one-half the resting heat production of the body when the ambient temperature is -4°C .

EMOTION. In the middle ranges of flow, the circulation through the hand is often very sensitive to slight emotional stimuli; it may suffer a considerable transient reduction, lasting a minute or more, when a person enters the room, if a remark is made or a question in mental arithmetic posed (2), or if there is an unexpected noise. For this reason it is important to reduce disturbance to a minimum in experiments in which the blood flow to the hand (or foot) is measured. A

more prolonged emotional stimulus, such as is provided by mental arithmetic for 10 min under trying conditions, causes in persons with hyperhidrosis and in some normal persons an increase in the blood flow through the hand; this is associated with emotional sweating (10). All these responses are prevented by division of the sympathetic nervous outflow. It is, however, possible that during more severe emotional upsets, the circulation through the skin may be affected by adrenal gland activity. In the forearm, the circulation through the skin is little affected by the emotional stress of mental arithmetic (76).

FAINING. In posthemorrhagic fainting the blood flow through the hand was found by Barcroft & Edholm (21) to be more reduced than would be expected from the fall in arterial blood pressure. This indicated vasoconstriction in the hand. Other observations have indicated little change or vasodilatation. It seems very probable that the response is a variable one, depending perhaps on the degree of associated emotional sweating. Little is known about the precise changes in blood flow in other areas of skin.

GENERAL SENSORY STIMULI. Transient reduction in hand or finger blood flow has been described in response to a great range of mildly unpleasant stimuli such as immersing another part of the body in cold water (160), pinching (2), or inflating a pneumatic cuff around the arm. On the other hand, Lynn & Simeone (146) were unable to provoke reflex vasoconstriction in anesthetized dogs by electrical stimulation or by distention of the femoral vein.

RESPONSE TO A DEEP INSPIRATION. After a deep inspiration there is a transient decrease in finger volume (38, 94). The size of the arterial pulsations diminishes and the rate of blood flow falls sometimes to a very low level (116, 189). The blood flow can be seen to slow in the capillary loops of the nail bed (153). The blood flow is similarly transiently decreased in the hands and feet (138) but not in the more proximal parts of the limbs. The response is lost after nerve block or sympathectomy.

Gilliatt (90) found that the vasoconstrictor response in the finger could be elicited by a sufficiently fast and deep expansion of the lungs, whether brought about by passive inflation or voluntary inspiration. It did not follow obstructed inspiratory or expiratory efforts, nor deep expiration. The response has been observed in the fingers and toes of persons with a complete break in the functional continuity of the

spinal cord above the level of the sympathetic outflow to the hands (91), and in these cases the response appears to be a purely spinal reflex. At least some of the afferent fibers must enter the cord below the second thoracic roots. The receptors and the precise nature of the effective stimulus have not been identified. The reflex may be responsible for the reduction in the blood flow through the hands in hyperventilation (2), but its functional significance is unknown.

RESPONSE TO DISTENTION OF THE BLADDER. Distention of the bladder causes a constriction of the blood vessels of the skin, and elsewhere, by a spinal reflex. The response was first described by Guttman & Whitteridge (111) in patients with complete transverse section of the spinal cord and in whom the isolated cord was undamaged. With sections above the level of the second lumbar outflow there was constriction in the skin of the feet and legs; with high section there was also constriction in the hands. The response may be sufficient to raise the arterial pressure, and to lead to consequent reflex adjustments in that part of the circulation innervated by the brain and upper part of the spinal cord. It is important when making observations on the skin circulation to start with the subject's bladder empty, and to re-empty it before it becomes uncomfortably full.

HYPOGLYCEMIA. The blood flow is increased through the hand and the forearm in insulin hypoglycemia (3). The increase in the forearm is partly in the skin, and mediated by an active vasodilator mechanism (11), probably associated with sweating. Injection of an adequate dose of atropine into the brachial artery reduces the blood flow through the forearm, but does not affect that through the hand (13).

POSTURE. Changes in body posture cause complex changes and reactions in the circulation, but if the inclination to the horizontal of the observed limb remains unchanged the net effect is that the circulation through the hands (27) and fingers and toes (131) is little changed. By contrast, as a single arm or leg is raised above the horizontal, the posture of all other parts remaining unchanged, the rate of blood flow through the digits is progressively diminished (174, 191) and in all dependent positions the blood flow is slightly increased (174). The digital pulse volume is greater in the raised limb, and less in the dependent limb, than it is in a horizontal limb (96). This is a striking example of the way in which, under some circumstances, blood flow and pulse volume may even

change in opposite directions, although in other circumstances their changes may correspond closely (42).

RESPONSES TO BARORECEPTOR STIMULATION. Present evidence suggests that the blood vessels of the skin are largely, and perhaps entirely, excused from participation in baroreceptor reflexes.

Low pressure baroreceptors. Unidentified low pressure baroreceptors within the thorax can be stimulated by raising the legs of a recumbent subject and allowing part of the blood they contain to flow into the central venous pool, or by breathing through a narrow tube which restricts air flow and causes intrathoracic pressure transients of +30 to -20 mm Hg to be set up. Such stimulation causes a reflex dilatation, brought about by reduction in vasoconstrictor nerve activity, in the blood vessels of the voluntary muscle of the forearm, but no change in the resistance to flow through the hand or through the skin of the forearm (173).

Systemic arterial baroreceptors. The decisive animal experiments, in which observations have been made on a perfused isolated innervated limb, while the baroreceptors have been stimulated in various ways (see 119), have dealt either with whole limbs or skinned limbs. There do not appear to have been any decisive experiments dealing with the skin as such. In the human, in experiments in which bilateral arterial compression caused increases in heart rate and arterial blood pressure (and was thereby shown to affect the baroreceptors), the vascular resistance through the hand remained unchanged (168).

ACTION OF HUMORAL AGENTS ON THE BLOOD VESSELS OF THE SKIN

The action of drugs on the skin has been recently reviewed by Herxheimer (118). Only substances of physiological importance will be considered here. Their direct local action is best tested by a steady intraarterial infusion. The dose is adjusted to the volume of tissue to which it will be distributed, and it is usually so small that any returning to the general circulation causes a negligible disturbance of arterial pressure and of the blood vessels elsewhere. By measuring the blood flow in the contralateral limb as well as in the infused limb general disturbances of the circulation can be detected and can be allowed for since these normally affect the limbs symmetrically.

The effect of humoral agents released into the

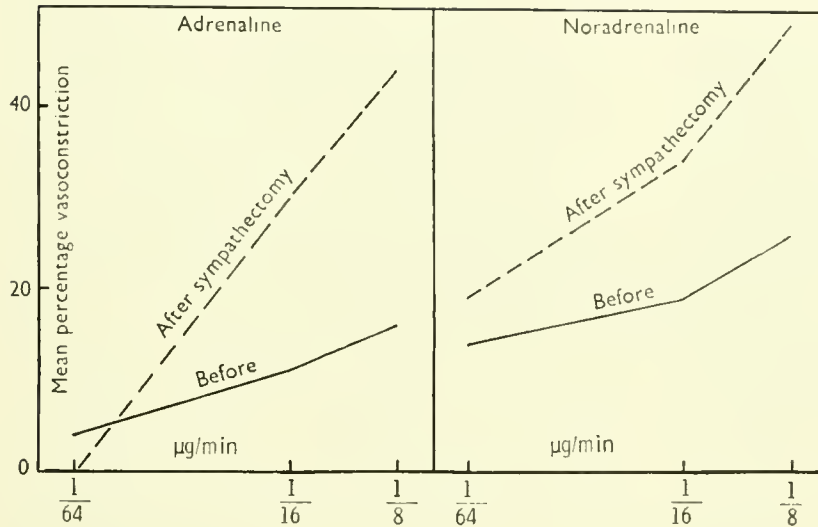


FIG. 14. The mean percentage reduction in the rate of blood flow in 13 hands, tested before and after sympathectomy, in response to infusions of adrenaline and noradrenaline at various rates into the brachial artery. The effects of general disturbance of the circulation have been eliminated by referring the blood flow to the simultaneously measured blood flow in the opposite hand. Noradrenaline has a greater constrictor effect than adrenaline in normally innervated hands. After sympathectomy the response to both substances is augmented. [From Duff (64).]

general circulation is tested by intravenous infusion. The rate should ideally follow the normal pattern of secretion but, in the general absence of exact knowledge of this, steady infusion is best employed (9) and is much superior to a sudden injection. The effect on the skin or any other part of the peripheral circulation depends on a combination of direct local action and of general circulatory disturbance involving changes in arterial pressure and vasomotor control, and probably changes in the concentration of other humoral agents in the arterial blood.

Adrenaline and Noradrenaline

Injected subcutaneously both substances cause intense local pallor, and iontophoresis of adrenaline can be used virtually to arrest the circulation through the skin (71). Injected into the brachial artery in very small doses, both substances (22) cause a reduction in blood flow through the hand (fig. 14). There is constriction of the low pressure capacity vessels, presumably veins, as well as of the resistance vessels (93).

During the infusion of either substance intravenously at 20 μg per min there is a severe reduction, and sometimes nearly complete arrest, of the blood flow through the hands. After adrenaline injection, the flow usually increases for a time to above the resting level (182) and there is often a flushing of the face (17, 103). No such increase is seen in sympathectomized hands, or after intravenous noradrenaline, or either substance given intra-arterially (182).

Histamine

Pricked into the skin histamine causes a local wheal and a reddening of the skin or flare extending for a radius of 3 to 4 cm (139). The temperature of the skin is only slightly increased in the region of the flare (61, 139) and, although the content of blood is greatly increased, the increase in the flow is modest. Infused into the brachial artery, histamine has a dilator effect at all doses tested (fig. 15) and the skin becomes deeply flushed. The flush does not always cover all parts of the hand, and this illustrates a general difficulty with intra-arterial infusions. The injected material may not become thoroughly mixed with the arterial blood at the site of injection, and the artery may not be the exclusive supply to the area of tissue examined. Further, the pattern of distribution may vary with changes in the circulation.

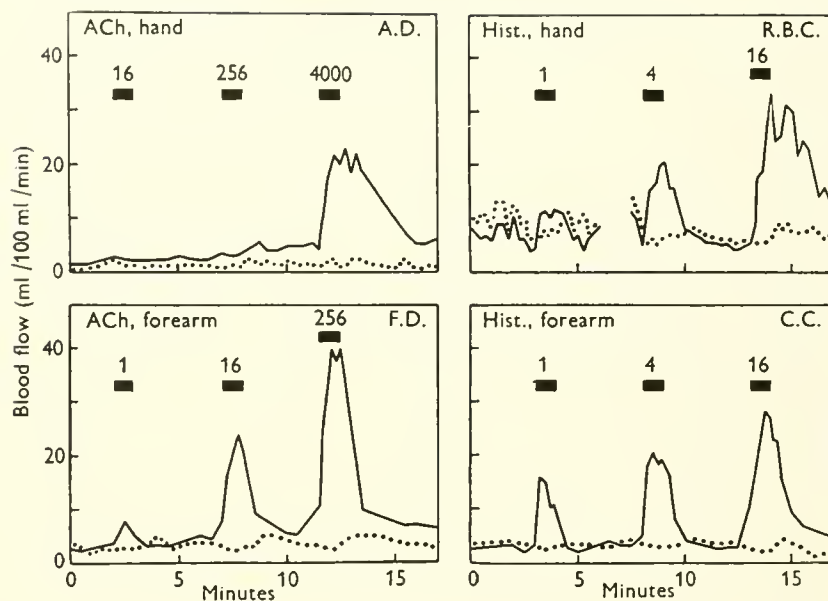
Acetylcholine

This acts as a powerful dilator to the blood vessels of the hand (fig. 15), but so rapid is its destruction in the blood stream that for equal effect on the blood flow through the hand the dose into the brachial artery must be about one thousand times as great as that into the radial artery (65).

5-Hydroxytryptamine (Serotonin)

When infused into the brachial artery at the rate of 1 μg per min or more, this causes a reduction in the rate of flow of blood through the hand, but the volume of the part increases because of edema forma-

FIG. 15. The effect on forearm and hand blood flow of various doses of acetylcholine and histamine injected over 1-min periods into the brachial artery of four normal subjects. Continuous line: injected side; dotted lines: control side. Doses in μg . [From Duff *et al.* (65).]



tion, and the skin becomes flushed and petechial hemorrhages appear; thus the vessels controlling flow are constricted, and those responsible for color are dilated (169). On the other hand, the low pressure capacity vessels as a whole are rendered less distensible (93), so the reaction of those responsible for color appears not to be typical of the low pressure vessels as a whole.

Adenosine Triphosphate

Injected intra-arterially in man, magnesium adenosine triphosphate causes a great increase in the blood flow through the hand, and is nearly as effective as an equal weight of histamine (68). A dose of 1 mg per min into the brachial artery raises the blood flow in the hand to an average value of 34 ml per 100 ml of hand per min. Adenosine triphosphate may be the transmitter substance released from sensory nerve endings causing antidromic vasodilatation (122).

Bradykinin

Detailed information is not yet published but it appears that, per molecule of injected substance, bradykinin has a more potent vasodilator effect than any other tested substance (80).

Carbon Dioxide

Breathing mixtures containing high concentrations of carbon dioxide has a complex effect on the circulation, with great disturbance of vasomotor regulation. The local effect of carbon dioxide, as seen when a hand is immersed in a saturated solution of the gas (60) or when carbon dioxide mixtures are injected subcutaneously (61), is entirely vasodilator. The effect has not, however, been quantitatively defined in terms of the response to various tensions of the gas in the tissues.

Vasopressin

Infused intravenously this causes an initial vasoconstriction in the hands, which diminishes as the infusion continues (133).

Oxytocin

Injected intravenously in man this may cause flushing. Injections of 500 units intravenously or 50 units into the brachial artery cause the blood flow through the hand to double for a few minutes. With repeated doses, by either route, the response diminishes (134). The vasodilator effect of oxytocin is balanced by one-twentieth of the number of units of vasopressin.

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Circulation in skeletal muscle

HENRY BARCROFT

*Sherrington School of Physiology, St. Thomas Hospital
Medical School, London, England*

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FEW WILL DENY that analytical study of the physiology of the circulation in skeletal muscle began in the Institute of Physiology at Leipzig. The paper bears the name of Gaskell (108), but it was Carl Ludwig who suggested the problem and who probably did many of the experiments. In Gaskell's Obituary Notice written by Langley (137) we read—"At this time Ludwig's laboratory was much the most important school of physiological research in Germany or elsewhere. It attracted students from all parts of the world. All the work was planned by Ludwig, who had an almost unerring sense of the lines of work which would yield profitable results. To this the success of the school was mainly due. Its popularity was increased by the method of procedure adopted by Ludwig. This has been described by T. Lauder Brunton who was with Ludwig in 1869-70. The experiments were carried out by Ludwig with the pupil as an assistant, Ludwig wrote the paper and then published it, occasionally as a conjoint work, but usually in the name of his pupil. As I have heard from Gaskell the method was the same in his time."

Be that as it may, let us turn to the experiments themselves—"On the changes of the blood stream in muscles through stimulation of their nerves." By a simple graphical method venous outflow was recorded from the extensor group of muscles of an unanesthetized dog. The changes in outflow were determined during and after tetanic stimulation of the crural nerve. From a typical record, such as that seen in figure 2 (top), six phases could be discerned during sustained contraction: *a*) an initial spurt due to squeezing of the veins by the muscles; *b*) decrease in flow caused to some extent by mechanical compression of the vessels by the contracted muscle; *c*) in-



FIG. 1. Walter Holbrook Gaskell, 1847-1914.

crease in flow; then, following contraction; *d*) a check in the rate of the stream while the veins refilled; *e*) a further large increase in flow; and finally *f*) gradual restoration of the flow to the resting rate.

It is interesting to compare Gaskell's record with that seen in figure 2 (bottom), which was made by Kramer & Quensel (131) 50 years later. They determined the venous outflow of the dog's gastrocnemius with a hot-wire anemometer. Kramer and his colleagues recognized the following changes in outflow during maximal tetanic stimulation of the motor nerve: *a*) an initial peak due to expression of blood; *b*) decrease in flow due to mechanical compression; *c*) increase in flow; then, after relaxation, *d*) transitory decrease while the vessels refilled; *e*) hyperemia reaching the maximum; *f*) restoration of the flow to the resting rate. The agreement between Gaskell's and Kramer's records is remarkable, the main difference being that the postexercise flow was greater in Gaskell's experiment. Presumably in his experiment the muscle had contracted more powerfully during stimulation.

So much for tetanic contraction. Figure 22 shows the changes during rhythmic contraction. The record is from another experiment of Kramer's (132). The motor nerve to the gastrocnemius was stimulated for 1 sec every alternate sec for 5 min. Venous outflow increased rapidly during the first minute to reach a steady level. Further increase in outflow occurred immediately after the exercise because the stream was no longer checked repetitively by mechanical compression. Then after a few seconds it subsided to the resting rate.

In man the changes in flow in the forearm muscles

during strong sustained contraction were determined by Grant (113), who recorded the rate of the blood flow by venous occlusion plethysmography. An excellent description of the method has been published by Greenfield (114). Grant's subject gripped an iron bar as hard as possible for 1 min. There was a small increase in flow during the exercise and a large one afterward. The vasodilatation during contraction was not conspicuous because of compression of the vessels by the contracted muscle. As soon as the muscle relaxed, compression ceased and then blood flowed rapidly into the veins.

During strong contraction of the human gastrocnemius soleus the effect of mechanical compression of the muscle vessels may stop the flow. For example, when one is standing tiptoe on the ball of one foot, supporting the whole weight of the body by contraction of the calf muscles, the blood flow in these muscles is probably arrested. This was inferred from records of the changes in temperature in these muscles made while the subject was standing on tiptoe (28). The length of time one can stand tiptoe on one leg

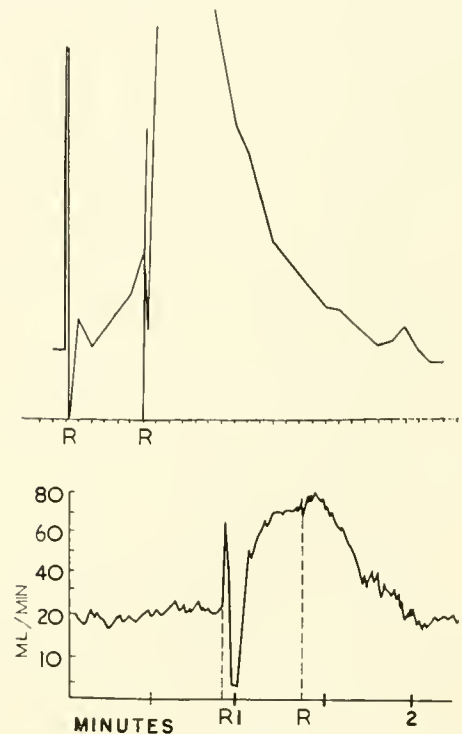


FIG. 2. *Top:* Changes in venous outflow from the extensor group of muscles of the dog's leg, during (R-R) and after tetanic stimulation of the crural nerve. [From Gaskell (108).] *Bottom:* Changes in the venous outflow from the gastrocnemius muscle of the dog recorded during (R-R) and after tetanic stimulation of the sciatic nerve. [From Kramer & Quensel (131).]

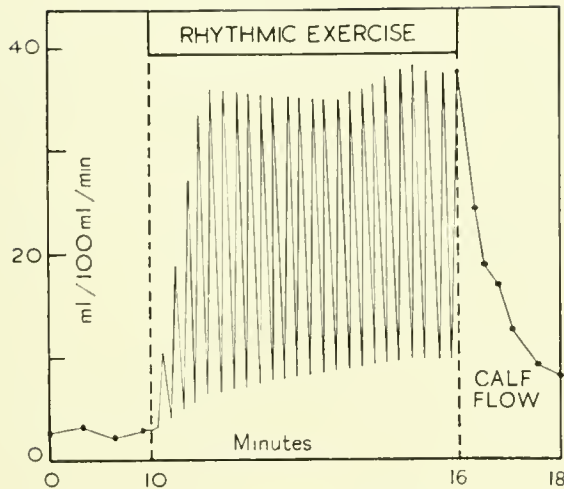


FIG. 3. Diagrammatic representation of changes in blood flow in the calf muscles of the human leg during strong rhythmic contraction. [From Barcroft & Dornhorst (19).]

is not curtailed by previous arrest of the circulation in the thigh. That is to say, the circulation in the calf is of no functional significance in tiptoe standing, an observation in accord with the fact that the gastrocnemius soleus arrests its own circulation when standing on tiptoe (28). During this exercise intramuscular pressure in the calf does not exceed about 50 mm Hg (119), so that it seems likely that the blood supply to the muscle is stopped by nipping of its vessels.

The circulation in the calf muscles behaves quite differently during weak sustained contraction. Then there is marked hyperemia. The effect of the vasodilatation predominates (28). The behavior of the circulation during the sustained contraction of other human muscles also depends upon the force of their contraction and the extent to which vasodilatation overcomes the effect of mechanical compression (67, 141, 142, 145).

When human muscles contract rhythmically, each strong contraction checks the hyperemia (19). This is shown in figure 3. In running, blood flow through the calf must be intermittent; free flow through widely dilated vessels when the muscles are relaxed must alternate with partial or perhaps complete arrest of the circulation during contraction.

Black (36) has investigated the effect on the post-exercise blood flow of walking at different speeds from 1 to 8 mph. The subject wore a light celluloid plethysmograph on his calf. The distance covered was 130 yards. Up to 4 mph the size of the immediate peak postexercise blood flow was directly proportional to the speed. The flow returned rapidly to its

resting value. At speeds of from 4 to 8 mph there was no further increase in the size of the peak post-exercise flow, but the flow returned to the resting rate more and more slowly as the speed increased.

These opening paragraphs recall the circulatory changes in muscle that take place during the performance of its most important function—namely, contraction. The mechanism of the hyperemia of exercise is not yet understood and it is the most important problem in this field. Besides dealing with the hyperemia of exercise this article must refer to many other matters. For example, we shall have to deal with the basal tone of the vessels, and with their nervous regulation, their responses to adrenaline, and so forth. It will be convenient to refer first to these general matters, and afterward, with such knowledge as a background, to return to the central problem of the hyperemia of exercise.

BASAL TONE

Skeletal muscle vessels exhibit a very pronounced basal tone. In this respect they differ from the vessels of the skin, or at any rate from the A-V anastomoses in the skin. Löfving & Mellander (143) found that the resistance to flow in acutely denervated cat muscles can be decreased by 80 to 85 per cent by the close arterial injection of supramaximal amounts of acetylcholine or ATP; the resistance in the denervated paw can only be decreased by 20 to 50 per cent.

The action of a circulating vasoconstrictor substance has often been invoked to explain the strong basal tone in muscle vessels. If this were so then constrictor substances such as noradrenaline, adrenaline, serotonin, angiotonin, and vasopressin should act more powerfully in muscle, where basal tone is strong, than in the skin where basal tone is weak. However Löfving & Mellander (143) have shown that many constrictor substances act more powerfully on the skin vessels of the paw than on skeletal muscle vessels. They concluded that the basal tone in muscle vessels cannot be due to the action of adrenaline, noradrenaline, serotonin, angiotonin, or vasopressin since muscle vessels did not respond more sensitively to any of these agents.

Human muscle vessels, too, exhibit strong basal tone. Vascular resistance in the normal forearm is about the same as that in the chronically sympathectomized forearm (73) and in both it decreases to about one-tenth in severe exercise (113). If the smooth muscle coats of these vessels were to stop

contracting spontaneously peripheral resistance and arterial blood pressure might well fall to a dangerously low level. Our very lives must depend upon the maintenance of basal tone in the vessels of the skeletal muscular system.

Automaticity

This may be illustrated by experiments on the cat. Folkow & Löfving (97) recorded the effect of lowering and then raising the arterial pressure upon the blood flow through the muscles of the leg and the following results have been calculated, approximately, from one of their experiments:

| | | | | | |
|-----|-----|-----|-----|-----|-----|
| ABP | 120 | 50 | 50 | 120 | 120 |
| F | 7 | 2.6 | 3.8 | 15 | 7 |
| PRU | 17 | 19 | 13 | 8 | 17 |

When the arterial pressure was suddenly lowered from 120 to 50 mm Hg the resistance to flow increased slightly from 17 to 19 units, probably because of elastic recoil of the vessels. Now over the next few minutes, arterial pressure being still 50 mm Hg, vascular resistance gradually fell from 19 to 13 units indicating a gradual reduction in smooth muscle tone. When the arterial pressure was suddenly restored to 120 mm the resistance fell from 13 to 8 units, due to stretching of the relaxed vessels. In the course of the next few minutes the resistance rose again from 8 to 17 units, its initial value, indicating a gradual restoration of smooth muscle tone. In short, lowering the arterial pressure was soon followed by decrease in basal tone and vice versa.

An even more striking example of automaticity is shown in another of Folkow's (89) experiments. Clamping the carotid arteries was followed by a rise in arterial pressure from 100 to 150 mm Hg; blood flow in the denervated muscular portions of the hind parts rose initially but soon returned to its initial level. In spite of the rise in arterial pressure, the lumen of the muscle vessels must have decreased.

The explanation of automaticity is not yet complete. Plain muscle responds to stretch by increased contraction. Bayliss (35) pointed out the significance of this. In a well-known experiment he recorded volume changes in the dog's hind leg before, during, and after splanchnic nerve stimulation. He notes: "As the arterial pressure rises the limb is distended passively, but instead of merely returning to its original volume when the blood pressure has come down again it constricts much below its previous level and only gradually returns." He thought this

was probably because the plain muscle of the arterial walls had responded to stretch by contraction. However, other factors may be involved. It will be remembered that when in one of Folkow's experiments described above the arterial blood pressure was raised the flow remained constant and the lumen of the vessels became smaller. In that case the stimulus cannot have been simply stretching the vessel walls if by that is meant a maintained elongation of the smooth muscle fibers. Nor can the vasoconstriction have been due to the lowering of metabolite concentration due to more rapid flow—in this experiment the flow did not increase. Perhaps some of the capillary bed shut down so that the same total quantity of blood flowed faster through a restricted area. Further work is needed on the fundamental significance of automaticity.

Pressure-flow relations in muscle depend a good deal on the condition of the animal. As this deteriorates in the course of an experiment, automaticity declines and the effect of alteration in arterial pressure upon muscle blood flow becomes more pronounced.

Automaticity in Human Muscle Vessels

Experiments by Greenfield & Patterson (115) show that human vessels constrict when they are stretched. The forearm was enclosed in a plethysmograph, for measuring the rate of flow, modified so that pressures of -50 and -150 mm Hg could be applied for 30 sec to the enclosed limb segment. Immediately after the release of the negative pressure forearm blood flow was decreased; the vessels must therefore have constricted. The vessels in the calf respond in the same way to stretching (60). Blair and others (38) recorded the oxygen saturation changes in blood from the skin and from the muscle. When suction was applied oxygen saturation rose at once in the blood from the skin and muscle, due to distention of the vessels. This can be seen in figure 4. However, by the end of the first few minutes of suction, oxygen saturation of the blood from both skin and muscle had returned to its initial value or was even less; thus the vessels had contracted to their initial size or even smaller. So much for the facts. Since the circumferential size of the vessels was not increased, and may have been decreased, the authors thought that the response could not be explained simply by stretching.

Stretching the vessels of normal, sympathectomized, and chronically denervated forearms by venous con-

gestion instead of by suction is also followed by constriction of the resistance vessels (157).

Pressure-Flow Relations in Muscle Vessels Deprived of Automaticity

Folkow & Löfving (97) investigated pressure-flow relations in maximally dilated muscle vessels in which automaticity had been abolished by perfusing

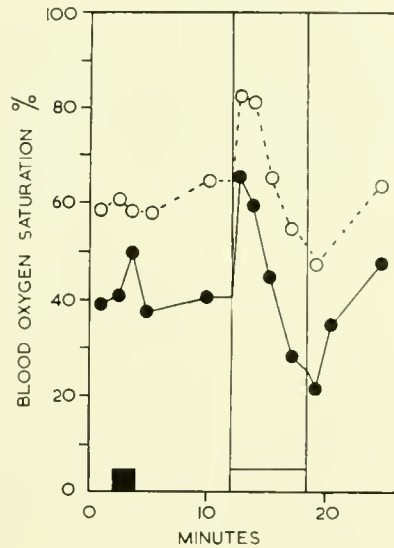


FIG. 4. Results showing that stretching of the forearm vessels causes contraction. Oxygen saturations of blood samples from a superficial (O) and a deep (●) forearm vein after general body heating. During the time represented by the black rectangle the subject's legs were passively raised. During the period between the vertical lines the forearm was exposed to a pressure 50 mm Hg below atmospheric. [From Blair *et al.* (39).]

them with dextran-Tyrode solution. Their results are summarized in figure 5. Figure 5A (continuous curve) shows the pressure flow relations when the arterial pressure was increased stepwise, the venous pressure being maintained at zero. The curve is convex to the pressure axis indicating vascular distention as the pressure increased, until further distention is prevented by the connective tissue and the development of edema. In Figure 5A (broken line) are seen the results when the mean intravascular pressure was kept constant at 50 mm Hg, and the perfusion pressure was increased by increasing the arterial pressure above and decreasing the venous pressure below the mean value. The relation between the perfusion pressure and the flow is then linear. This is as would be expected since the distending force, and hence the resistance to flow remain constant at all values of the perfusion pressure. Finally in Figure 5B is seen the effect of raising arterial and venous pressures together by equal increments so that the perfusion pressure remains constant while mean pressure increases. It will be seen that the greater the mean pressure the larger is the flow corresponding to a given difference in the perfusion pressure. This follows because an increase in the mean pressure distends the vessels and decreases intravascular resistance. When the mean pressure is high the vessels are almost maximally distended and resist further distention like rigid tubes.

Critical Closing Pressure

When the arterial supply to the cat's muscles was occluded in an animal in good condition the arterial pressure did not level out at a value specific for the

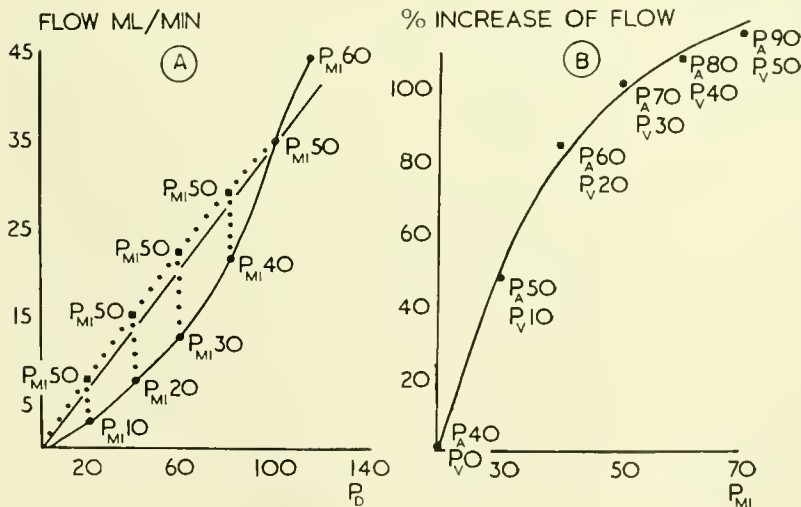


FIG. 5. Perfusion of the calf of the cat's leg with dextran-Tyrode solution. Vessels maximally dilated. Arterial pressure, P_A ; venous pressure, P_V ; perfusion pressure, $P_A - P_V = P_D$; mean pressure, $\frac{P_A + P_V}{2} = P_M$. For further explanation see text. [After Folkow & Löfving (96).]

prevailing vascular tone (97), that is to say, not when the muscle vessels exhibited automaticity. On the contrary, the arterial pressure always fell to within a few mm Hg of zero. During the occlusion basal tone must have decreased, as was manifested afterwards by reactive hyperemia. Observations in man confirm this. After arrest of the circulation in the upper arm, intrabrachial arterial pressure and pressure in the antecubital vein fall progressively till eventually intra-arterial sinks below intravenous pressure. This is explained by progressive loss of intravascular tone, without however the reflux of venous blood, which is prevented by the action of the venous valves (48).

Using a pressure plethysmograph, Burton & Yamada (48) found that the vessels of a segment of the forearm did close critically after reduction of their transmural pressure. About half the tissue in their forearm plethysmograph must have been muscle. Further work is needed on critical closing pressure in healthy muscle.

Local Temperature

Not enough is known about the effect of local temperature on the blood flow through muscle. Blood flow appears to decrease progressively when the cat's hind limb with paw tied off is cooled from 40 C to 25 C. Further cooling is accompanied by increase in flow which at 10 C generally exceeds that at 40 C (155). This is not so in the limb that has been treated with cyanide: blood flow diminishes as the temperature falls, owing to diminution in the fluidity of the blood (155).

In man the average forearm blood flow when the limb was in water at 45 C was 17.6 ml per 100 ml per min. When the water was 13 C forearm flow was 0.5 ml. However, these experiments tell us little about the effect of local temperature on human muscle blood flow (20). Forearm blood flow increases as the temperature of the surrounding water is lowered from 18 C to 0 C; the dilatation is mainly in the muscles as it takes place after the circulation in the skin has been arrested by adrenaline electrophoresis. Further work in this field is needed.

THE PROBLEM OF STRUCTURE AND FUNCTION

The arrangement of blood vessels in striated muscle was studied by Spalteholz (173) and described as follows by Krogh (134). "The arteries

supplying a muscle branch freely, and between the branches there are very numerous anastomoses forming a primary network. Into the meshes of this net small arteries are given off at regular intervals, and these again anastomose freely, forming a secondary cubical net of great regularity. From the threads of this network the arterioles branch off, generally at right angles to the muscle fibers and at very regular intervals (of about 1 mm in the warm-blooded animal), and these arterioles finally split up into a large number of capillaries running along the muscle fibers and in the main parallel to them but with numerous anastomoses, forming long narrow meshes about the fibers. The capillaries unite into venules intercalated regularly between the arterioles, and the whole system of veins reproduces and follows almost exactly that of the arteries. All the veins down to the smallest branches are provided with valves allowing the blood to flow in the direction of the heart only."

The number of capillaries per square millimeter transverse section of striated muscle is related to the metabolic activity of the animal. Krogh found 400 per mm² of muscle in the cod, 1350 in the horse, 2630 in the dog, and the number in the smallest mammal he thought would be more than 4000. Assuming a figure of 2000 for the number of capillaries per square millimeter of human muscle he calculated that the total length of all the capillaries in all the skeletal muscles of a man would be equal to a distance of two and a half times round the earth, and he estimated that when all these capillaries were open their surface area would be 6300 m².

Certain experimental findings are difficult to explain on the basis of the classical description of skeletal muscle vessels. For example, stimulation of the vasoconstrictor nerves to the dog's hind legs is accompanied by decrease in muscle blood flow, by decrease in oxygen consumption of the muscle and surprisingly by a rise in oxygen saturation of the venous blood (154). Pappenheimer thought that the blood must have been directed through A-V shunts whose surface area available for O₂ exchange was small. Issekutz (127-129) came to the same conclusion. Then, again, increase in muscle blood flow is accompanied by decrease in oxygen consumption during sympathetic vasodilator nerve stimulation (126), but by increase in O₂ consumption during inhibition of sympathetic vasoconstrictor tone (169). As figure 6 shows, hypothalamic stimulation is accompanied by increase in venous outflow from muscle but the clearance of NaI¹³¹ from muscle does not alter. To explain such results it has been suggested

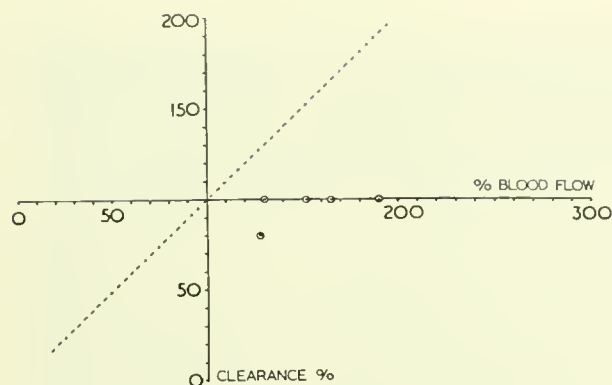


FIG. 6. Radio-iodide clearance and blood flow in the gastrocnemius: NaI^{131} injected intra-arterially. Results show that hypothalamic stimulation increases muscle blood flow but does not alter NaI^{131} clearance. \circ —Stimulation of the hypothalamic vasodilator pathway; 5 trials, 4 cats. [From Hyman *et al.* (126).]

the stimulation of the vasodilators shifts the flow from nutritional to nonnutritional (A-V shunt) channels.

Intravenous infusions of adrenaline increase the rate of the blood flow through muscle without affecting the rate of Na^{24} clearance (151). This too has been attributed to the opening of A-V shunts (18). A-V anastomoses have been invoked to explain the circulatory changes in muscle during hypothermia (61) and to account for the very small A-V O_2 difference in resting muscle (31).

Zweifach (181) claims that he has seen blood short-circuiting through "thoroughfare vessels" in skeletal muscle, and Redish *et al.* (161) have published photomicrographs of A-V shunts in human skeletal muscle. However, most anatomists deny the existence of A-V anastomoses in skeletal muscle (43). The perfusion of skeletal muscles with fluids containing minute plastic spheres shows, moreover, that no sphere of $30\ \mu$ diameter or over traverses the denervated gastrocnemius of the dog, though one-fifth of the stream goes through vessels of $20\ \mu$ diameter. These vessels may be large capillaries (66, 159).

Barlow *et al.* (32, 33), having failed to find A-V shunts in muscle, have suggested another explanation of the action of adrenaline on the muscle circulation. They found that muscle contains two entirely separate circulations, one to the skeletal muscle fibers, the other to the connective tissue. According to these authors adrenaline increases the rate of flow through the nutritional vessels as is shown plethysmographically. However, it has little effect upon the rate of flow in the connective tissue where, in most experi-

ments, the Na^{24} is located, so that the rate of Na^{24} clearance is scarcely altered.

Folkow (93) and Mellander (149) are using the following scheme for the muscle circulation. After large "windkessel vessels," which transform pulsatile into fairly steady flow, come "resistance vessels," consisting of two variable sets—precapillary (predominantly the arterioles) and postcapillary (mainly the small veins). These vessels determine the resistance to flow and also affect the hydrostatic capillary pressure and therefore the filtration rate. The "sphincter" vessels are a specialized section of the smallest precapillary resistance vessels. These vessels can cause intermittent closing of the capillaries and they regulate the size of the capillary surface area exposed to the blood flow and available for blood-tissue fluid exchange. Then there are "capacitance vessels" (mainly the veins) in which minor changes in tone, too small to affect the resistance significantly, will have a large effect upon the circulating blood volume available for the heart. Lastly there are, of course, the "exchange vessels" or true capillaries for the direct exchange of substances between the blood and tissue fluids; they are devoid of smooth muscle cells.

Further work is necessary to reconcile the function of the vascular bed in muscle with its structural arrangement.

NERVOUS CONTROL

Skeletal muscle vessels exhibit strong intrinsic basal tone and correspondingly weak nervous control. Their smooth muscle is supplied by sympathetic vasoconstrictor and vasodilator fibers, though the belief that these act reciprocally is no longer tenable. Nor is there at present any convincing evidence that muscle's sensory innervation has any effect on its vessels, either by antidromic impulses or by axon reflexes.

Sympathetic Vasoconstrictor Nerves

These have been found in the cat, dog, hare, monkey, and in man, in fact in all mammals so far investigated [for literature see 29, 92]. The evidence for their existence in animals is conclusive. It may be of some interest to refer briefly to the proof of their presence in man (21, 29). It is as follows. The rate of the blood flow in the upper muscular parts of both forearms was measured plethysmographically and

found to be equal. Radial, median, and ulnar nerve blocks were performed in one arm, above the elbow, and the rate of the blood flow doubled in that limb. Nerve blocks did not affect the rate of the blood flow in the sympathectomized forearm. Therefore the doubling of the flow in the normal forearm must have been due to blocking sympathetic vasoconstrictor fibers. Whereabouts were the vessels supplied by these fibers? Nerve block doubled forearm blood flow after the circulation in the skin had been arrested by adrenaline electrophoresis. Therefore the release of vasoconstrictor tone was deep to the skin, probably in the skeletal muscles. Other authors have confirmed this (166). It is interesting to note that brachial plexus block is followed by an even greater increase in forearm flow (23). Release of vasoconstrictor tone in all muscles would increase the circulation through the skeletal muscular system by 1.5 liter per min—the increase in severe exercise is far greater, about 20 liter per min (21). Sympathetic vasoconstrictor tone is also present in the resting muscle of the cat (13), dog (10), and man (21), and probably in the muscle vessels of all other mammals.

EFFECT OF SYMPATHETIC VASOCONSTRICTORS UPON RESISTANCE, BLOOD VOLUME, AND CAPILLARY FILTRATION IN SKELETAL MUSCLE VESSELS. So far we have seen that the vasoconstrictor fibers in muscle can increase

the resistance to flow. They can also reduce capillary filtration and increase venous constrictor tone. A beautiful preparation shown in figure 7 has been developed by Mellander (149) for simultaneous recording of these effects. These studies will be briefly described. They concern the effects of stimulation of the abdominal sympathetic chain upon the circulation in the hind parts of the cat—almost the whole of the cat distal to the fifth lumbar vertebra. This part of the cat consisted of skin, muscle, and bone in the proportions of 1:4:1. The circulation through bone could be neglected and the hind parts could be regarded as a "combined skin-muscle region," a few experiments with rather similar results were made on skinned hind parts or "muscle regions." Figure 8 shows a typical tracing. The arterial inflow pressure was maintained constant, by means of a screw clip, at 120 mm Hg. Atropine was given to exclude the action of the vasodilator fibers. The abdominal sympathetic was stimulated for periods of 1 min, indicated by the signal marker, at the different frequencies shown on the tracing. The tracing also shows the corresponding changes in the volume of the hind parts, which were enclosed in a plethysmograph communicating with a piston recorder. During stimulation the hind parts shrank rapidly at first and then more slowly. The initial rapid shrinking, shown by an almost vertical downstroke of the lever,

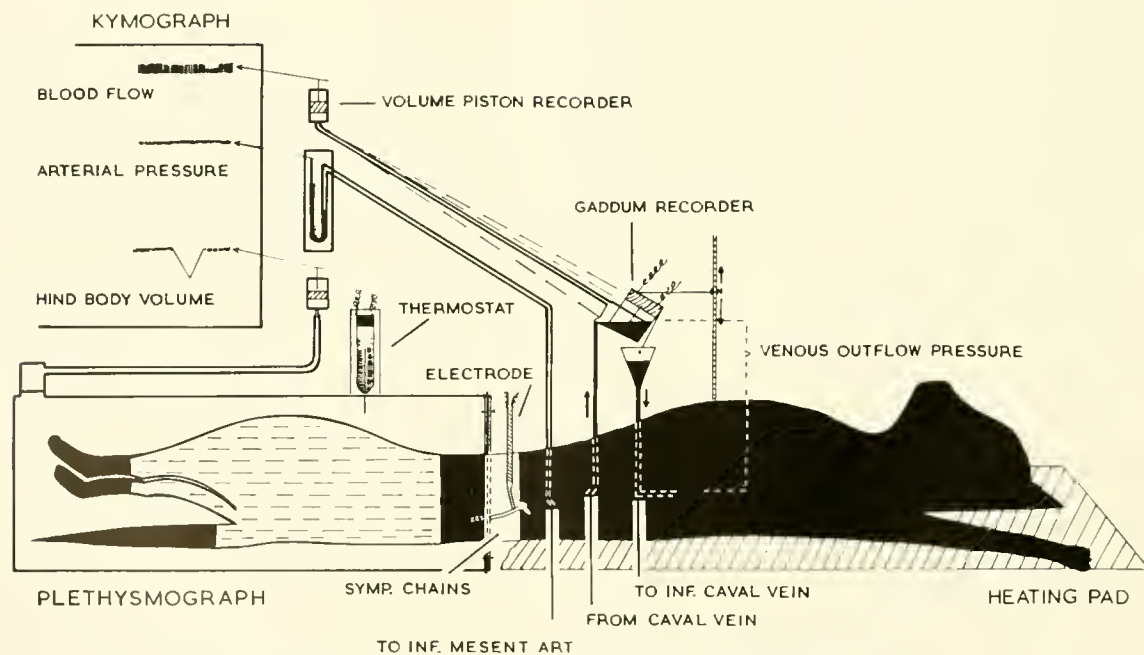


FIG. 7. Preparation used by Mellander to investigate the effect of sympathetic vasoconstrictor nerve stimulations upon vascular resistance, blood volume and capillary filtration rate in skeletal muscle vessels. [After Mellander (149).]

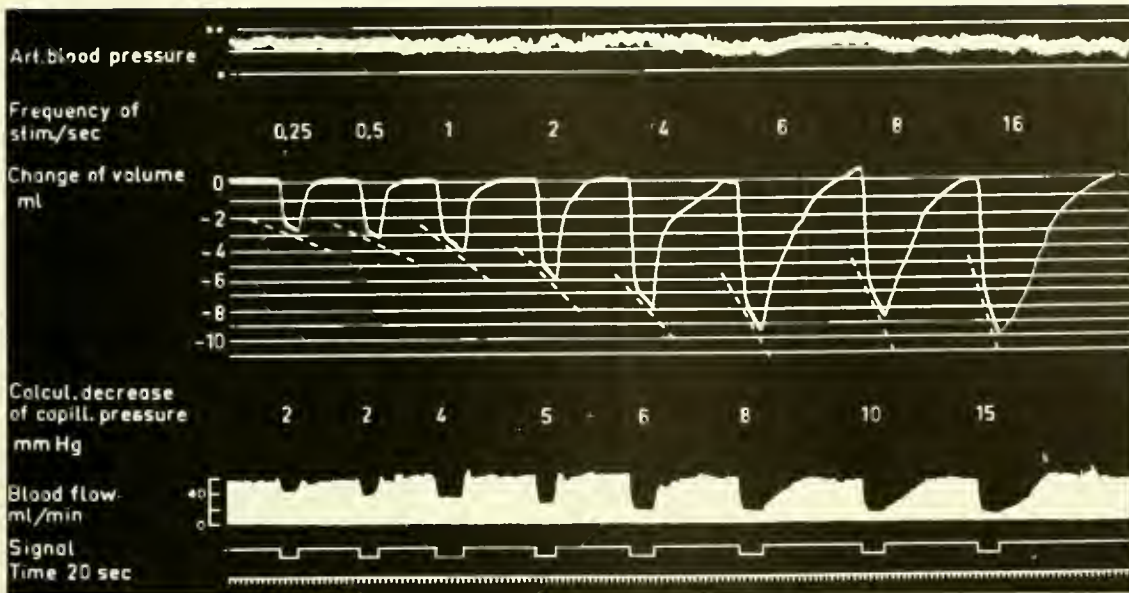


FIG. 8. Typical tracing obtained by Mellander using the preparation shown in fig. 7. For further explanation see text. [After Mellander (149).]

was a measure of the decrease in the volume of blood in the hind limbs, mainly due to contraction of the venules. The subsequent slower shrinkage, indicated by the dotted sloping lines, was a measure of the rate of loss of tissue fluid. Below the record of the volume changes are shown the corresponding changes in capillary pressure; these were calculated after the experiment and will be referred to later. Below this again we see the changes in the venous outflow from the hind parts, the rate of flow is proportional to the height of the record. At the beginning of the experiment the venous pressure was adjusted, by raising or lowering the venous outflow cannula, so that the volume of the hind parts remained constant. It will only be necessary to consider the change in the circulation produced by sympathetic nerve stimulation at 2, 8, and 16 impulses per sec. Typical results are shown in table 1. The data obtained from the tracing are shown by the figures in *italic*, namely the arterial blood pressure (line 1); the capacitance changes (initial rapid shrinkage, line 8); the rate of loss of tissue fluid (slow continuous shrinkage, line 12) and the rate of the venous outflow (line 2).

It will be convenient to consider first the changes in resistance due to the effect of the vasoconstrictors in the precapillary and postcapillary vessels, that is mainly on the arterioles, and to a smaller extent on the venules. Maximal vasoconstriction was produced by stimulation at frequencies of 16 per sec or more.

The outflow decreased from 60 to 10 ml per min (line 2), a reduction of 50 ml (line 3) which can be regarded as 100 per cent maximal (line 4). This corresponds to a 6-fold increase in resistance (line 5), an increase of from 2 to 12 P.R. units (line 6).

However the maximum possible physiological impulse frequency, as we shall see, is probably not more than 6 to 10 per sec. The changes recorded using a frequency of 8 per sec are therefore of particular interest. The blood flow from the hind parts was reduced from 60 to about 13 ml (line 2), a reduction of about 47 ml (line 3), a response corresponding to 94 per cent of the maximal (line 4) and to a four-and-a-half-fold increase in resistance (line 5). These figures correspond to a reduction in the rate of flow in the hind parts from 8.5 ml per 100 ml hind part per min to 1.85 ml per 100 ml per min (hind-part volume 700 ml).

We must now refer to the effects of stimulating the vasoconstrictor nerves upon the volume of blood in the vessels of the hind parts. The maximal effect was obtained at a frequency of 8 per sec. At this frequency, 6.25 ml were expelled by venous contraction (table 1; line 8). According to this the amount of blood that could be expelled by venous contraction from the whole of the skin and the entire skeletal muscular system, tissues weighing half as much as the whole body, would be only 4.5 per cent of the animal's blood volume. But of course it must be

TABLE 1. *Changes in the Circulation and Tissue Fluid Volume in the Hind Limbs of the Cat During Stimulation of the Sympathetic Vasoconstrictor Nerves*

| | Before Stimulation | After 1 min Stimulation at the Following Frequencies | | |
|---------------------------------------------------------------|--------------------|------------------------------------------------------|-----------------|-----------------|
| | | 2 | 8 Max Physiol | 16 Max |
| 1 ABP, mm Hg | 120 | 120 | 120 | 120 |
| 2 Blood flow from hind parts, ml/min | 60 | 40 | 13 | 10 |
| 3 Decrease in blood flow, ml/min | | 20 | 47 | 50 |
| 4 Decrease in flow as % max decrease | | 40 | 94 | 100 |
| 5 Increase in resistance | | 1 $\frac{1}{2}$ | 4 $\frac{1}{2}$ | 6 |
| 6 Resistance, PRU | 2 | 3 | 9 | 12 |
| 7 Percentage shortening of plain muscle in resistance vessels | | | | 35 |
| 8 Decrease in blood volume of hind parts, ml | 0 | 5 | 6 $\frac{1}{4}$ | 6 $\frac{1}{4}$ |
| 9 Decrease in blood volume of hind parts as % of max | | 80 | 100 | 100 |
| 10 Blood loss as % of total blood in hind parts | | 25 | 33 | 33 |
| 11 Percentage shortening of plain muscle in venules and veins | | | | 20 |
| 12 Slow decrease in volume of hind parts, ml | 0 | 2 | 5 | 6 $\frac{1}{2}$ |
| 13 Decrease in capillary BP, mm Hg | | 5 | 10 | 15 |
| 14 Approximate capillary BP, mm Hg | 24 | 19 | 14 | 9 |

remembered that skin and resting muscle are relatively avascular tissues and only contain 14 per cent of the blood volume. Measurements of the volume of blood in the hind parts, by a radioisotopic method, showed that they contained about 20 ml of blood. Of this, 6.25 ml, that is 33 per cent, was expelled by sympathetic activity. If the sympathetic could expel 33 per cent, the same proportion, from the splanchnic area which contains a relatively enormous amount of blood, it is clear that this mechanism would be of great importance.

But let us return to table 1 and to Mellander's results. It will be seen that at 2 per sec hind-part blood volume is reduced by 80 per cent of the maximal (line 9) and that resistance is not reduced by 80 per cent until the impulse frequency has been increased to 8 per sec (line 4).

To account for the changes in resistance and hind-part blood volume found during maximal electrical stimulation Mellander has calculated that the internal circumferences of an "average arteriole" and an "average venule" would have to decrease by 35 per cent and 20 per cent, respectively. This would happen if the smooth muscle coat in both arterioles and venules shortened by 20 per cent. In the case of the arteriole, owing to the protrusion inwards of the inner wall layers (99), this would reduce the internal circumference not by 20 per cent but by about 35 per cent.

Table 1, line 12, shows the effect of sympathetic chain stimulation on transcapillary fluid movement. During stimulation tissue fluid entered the capillaries and drained away, the amount being related to the impulse frequency. The greater the impulse frequency the more must capillary pressure have fallen. The precapillary vessels must have constricted both absolutely and relatively more than the postcapillary vessels. The discrepancy must have increased as the frequency increased. The falls in capillary pressure corresponding to the different impulse frequencies were determined as follows. In a control experiment venous pressure was decreased by a known amount by lowering the venous cannula, and the rate at which fluid drained from the tissues out of the hind parts was recorded. From this the rate at which fluid entered the capillaries per 1 mm drop in capillary pressure was calculated. This was the absorption coefficient. Knowing both this and the rate of entry of fluid into the capillaries recorded during the stimulation at the different impulse frequencies, the corresponding falls in capillary pressure could be calculated. These are shown in lines 13 and 14 and in the tracing in figure 8.

Another interesting point is that at the end of 2-min stimulation the absorption of tissue fluid ceases. Nevertheless during maximal physiological sympathetic stimulation for 2 min the volume of tissue fluid draining out of the hind parts is almost as much as that expressed from the capacitance vessels (lines 8 and 12).

Folkow & Mellander (98) have developed a technique for investigating the effect of a procedure upon the capillary surface area. Maximal stimulation of the sympathetic vasoconstrictors, they find, closes many precapillary sphincters and reduces the capillary surface area to about one-third under conditions where blood flow is decreased to about one-sixth.

CHEMICAL TRANSMISSION AT SYMPATHETIC VASOCONSTRICTOR NERVE ENDINGS IN SKELETAL MUSCLE. Folkow

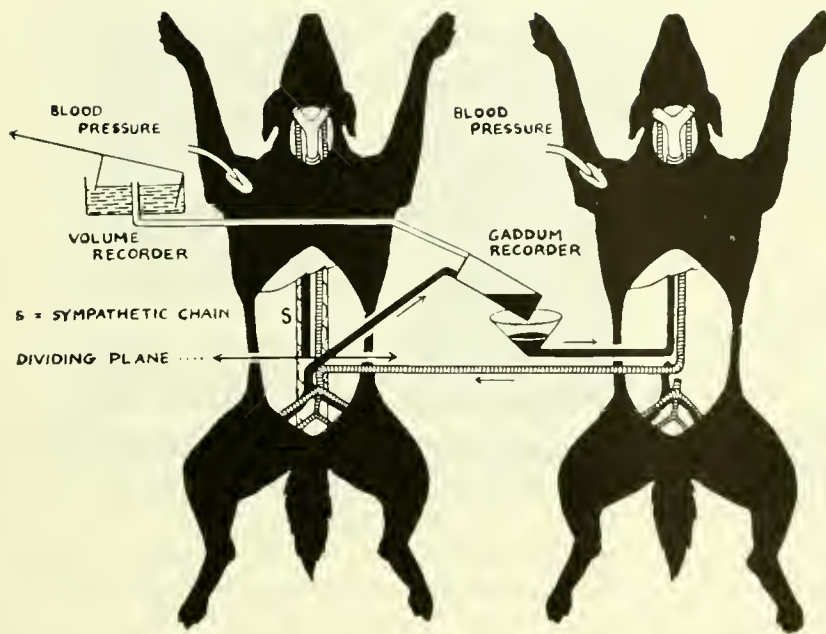


FIG. 9. Preparation used for investigating the effect of stimulation of the baroreceptors on muscle blood flow. [After Folkow *et al.* (101).]

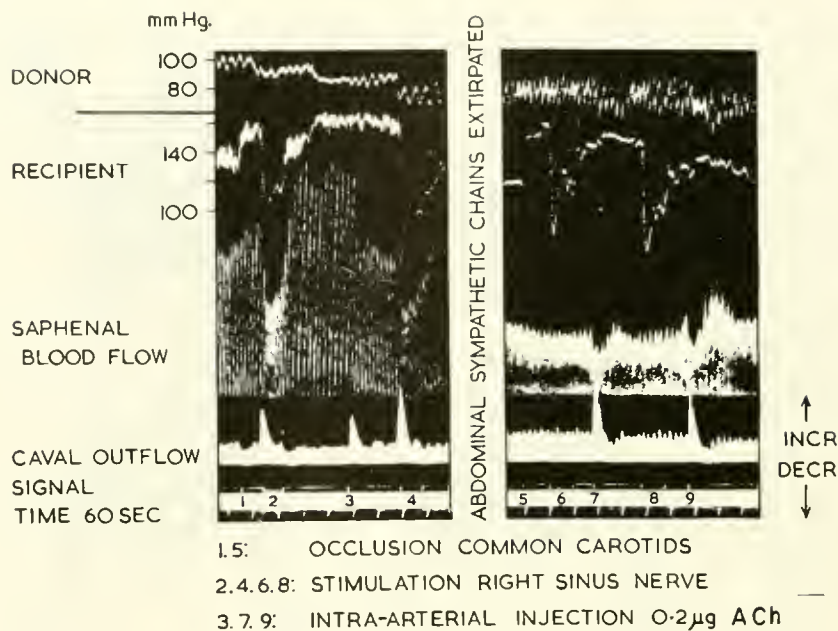
& Uvnäs (102, 104) have shown that the transmitter is probably noradrenaline. It is not adrenaline. Proof of this was obtained in cats given Dibenamine. Other procedures excluded the action of the vasodilator fibers. After giving Dibenamine, stimulation of the vasoconstrictors caused only weak contraction or none at all. Injections of noradrenaline likewise caused weak contraction or had no effect. On the other hand, injections of adrenaline caused marked vasodilatation in the muscle. From such results Folkow and Uvnäs concluded that the vasoconstrictor nerve endings in the muscles of the cat (102) and dog (104) might have released noradrenaline but they had not released adrenaline. For a proper account of these beautiful experiments and for the literature, their papers should be consulted. Noradrenaline has not yet been positively identified in the venous effluent collected from a muscle vein during vasoconstrictor nerve stimulation.

EFFECT OF STIMULATION OF THE ARTERIAL BARORECEPTORS ON SKELETAL MUSCLE VESSELS IN THE DOG. Folkow *et al.* (101) have shown that the sympathetic vasoconstrictor fibers are solely responsible for mediating the baroreceptor reflex. Their proof is as follows. Figure 9 shows the preparation of the hind parts of one dog (the recipient) which were perfused from another dog (the donor); changes in blood pressure and in hormone concentration in the upper part of the recipient's body could not affect the circulation

in its hind legs. The venous outflow from the hind legs, mainly from the muscles, was recorded, as was that from an area of the hind-leg skin. The results are seen in figure 10. Reduction of the blood pressure in the recipient's carotid sinuses, by carotid occlusion, caused vasoconstriction in both muscle and skin. After section of the abdominal sympathetic nerves neither carotid occlusion nor stimulation of the carotid sinus nerve had any effect whatsoever. Dorsal root fibers could not have been implicated. They could have mediated vasodilatation, as acetylcholine injections did. And they were still in good physiological condition because vasodilatation was recorded in the skin when the dorsal roots were stimulated (101). In other experiments the vasoconstrictor action of the abdominal sympathetic chains was blocked by Dibenamine. Clamping the carotids no longer caused vasoconstriction in the legs. Although the sympathetic vasodilator pathway remained intact there was no sign of reciprocal innervation. On the other hand, vasoconstriction in the legs following carotid occlusion was normal after the dilator fibers had been blocked by atropine (104). Folkow and his colleagues concluded that the effect of stimulation of the arterial baroreceptors on the blood flow in muscle must be mediated solely by inhibition of activity in the sympathetic vasoconstrictor fibers.

EFFECT OF STIMULATION OF THE ARTERIAL BARORECEPTORS ON THE CIRCULATION IN HUMAN SKELETAL

FIG. 10. Results obtained with the preparation shown in fig. 9. Sympathectomy abolished the action of the carotid sinuses upon the skin and muscle of the hind limb. [After Folkow *et al.* (101).] Note that an increase in saphenal blood flow records downward.



MUSCLE. Folkow and others (54) recorded the effect of stimulation of the carotid sinus nerve in five patients during block dissections of the neck performed for the treatment of cancer. Stimulation at 40 per sec elicited maximal effects. Mean blood pressure and pulse amplitude fell promptly, there was a slight increase in forearm flow, implying considerable vasodilatation, which was probably of nervous origin.

Nevertheless it is unlikely that arterial pressure changes in the carotid sinuses in man have much effect on the sympathetic tone in human muscle vessels for the following reasons. Stretching the carotid sinuses by applying subatmospheric pressure to the outside of the neck causes bradycardia and fall in arterial pressure—signs of stimulation of the baroreceptors—but vascular resistance in the forearm is unaltered (81). Compression of the carotid arteries, followed by fall of the carotid arterial pressure to 20 mm Hg causes tachycardia, hyperpnea, and rise in brachial arterial pressure—signs of decreased baroreceptor activity—but forearm vascular resistance is unaltered (163). Although strong stimulation of the carotid sinus nerve causes reflex vasodilatation in human muscle quite large changes in the transmural pressure in the carotid sinuses do not seem to have any effect on the vascular resistance in human muscle.

EFFECT OF RECEPTORS IN A LOW PRESSURE AREA IN THE CARDIO-PULMONARY SYSTEM ON THE SYMPATHETIC VASOCONSTRICTOR TONE IN HUMAN SKELETAL MUSCLE.

The evidence for this important reflex is as follows (39, 164, 167, 168). Raising the legs of a recumbent subject increases the forearm blood flow. It does not have this effect in the sympathectomized forearm. The dilatation is reflex. Raising the legs after the circulation in them has been arrested has no effect upon forearm blood flow. The reflex is elicited by a shift of blood from the legs into the trunk. Raising the legs has scarcely any effect on arterial blood pressure. We have already seen that in man neither stretching the carotid sinuses (81) nor reducing the blood pressure in them (163) affects the tone of blood vessels of the forearm—so it seems very unlikely that their discharge frequency would be affected by the very small change in arterial pressure which follows raising the legs. On the other hand, raising the legs increases the central venous pressure. It seems then reasonable that rise in pressure on the venous side stretches structures in the cardiopulmonary system and so stimulates low pressure receptors which reflexly increase forearm blood flow. This conclusion is supported by the finding that blood flow in the normally innervated forearm increases when the thoracic vessels are stretched by negative pressure breathing (39). When the thoracic contents are repetitively stretched by rapid alternating positive and negative intrathoracic pressure changes forearm blood flow is trebled or quadrupled (163).

The low pressure receptors act reflexly by altering sympathetic vasoconstrictor tone in the muscles. This has been deduced from the following observa-

utions. Raising the legs increases forearm blood flow but it has no effect on blood flow in the hand, which has very little muscle. The increase in forearm flow is accompanied by increase in oxygen saturation of the blood draining from the forearm muscles but there is no change in the oxygen saturation of the blood draining from the forearm skin. Therefore the vasodilatation in the forearm must be in the muscles. As mentioned previously, the reflex is mediated by the sympathetic nerves as it is absent in sympathectomized forearms and after deep nerve block. Atropinization of the forearm does not weaken it. Therefore vasodilator fibers do not seem to be implicated, and it is probably due to decrease in the discharge frequency in the vasoconstrictor fibers (167).

This low pressure receptor reflex in skeletal muscle vessels may function so as to reduce the effect of alterations in venous pressure upon the arterial blood pressure. The effect of an increase in venous pressure and cardiac output on arterial pressure would be reduced because of reflex vasodilatation in the muscles. Conversely reflex constriction in skeletal muscles would tend to maintain arterial blood pressure after a fall in venous pressure and cardiac output. After major operations forearm blood flow is decreased for several days (110). This may be due to a low pressure receptor reflex induced by hemorrhage and decreased venous pressure. The importance of low pressure receptor reflexes in man may be related to the upright posture.

IMPULSE FREQUENCY IN SYMPATHETIC VASOCONSTRICTOR FIBERS. Folkow (90) has also investigated the impulse frequency in the vasoconstrictor fibers to skeletal muscle—postganglionic C-fibers. He concluded that whereas in somatic fibers the maximum discharge frequency may reach 50 per sec the maximum frequency in the vasoconstrictors to muscle hardly ever exceeds 6 to 10 per sec, and normal sympathetic tone is maintained at a discharge frequency of only about 1 per sec. The experiments forming the basis of this statement are most elegant. The preparation is seen in figure 11 and a typical result in figure 12. Atropine was given to block the action of the vasodilator fibers. Venous outflow from the isolated muscles of one cat's leg was recorded before, during, and after 1-min periods of stimulation of the abdominal sympathetic chain at frequencies increasing stepwise from 0.5 to 20 per sec. As the frequency was increased the reductions of the blood flow became greater and were maximal at a frequency of 16 per sec. After stimulations at frequencies

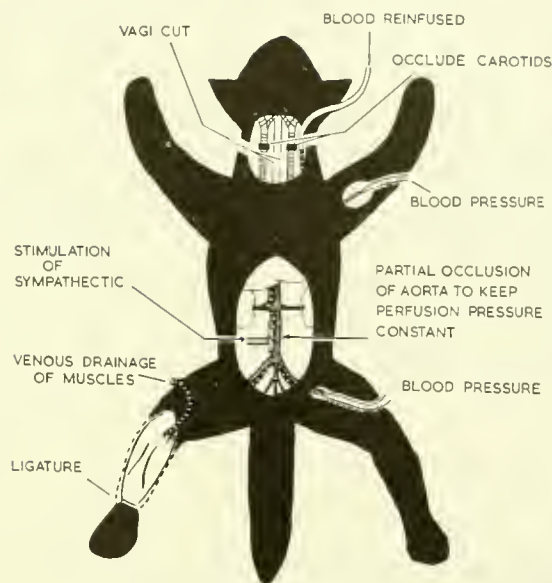
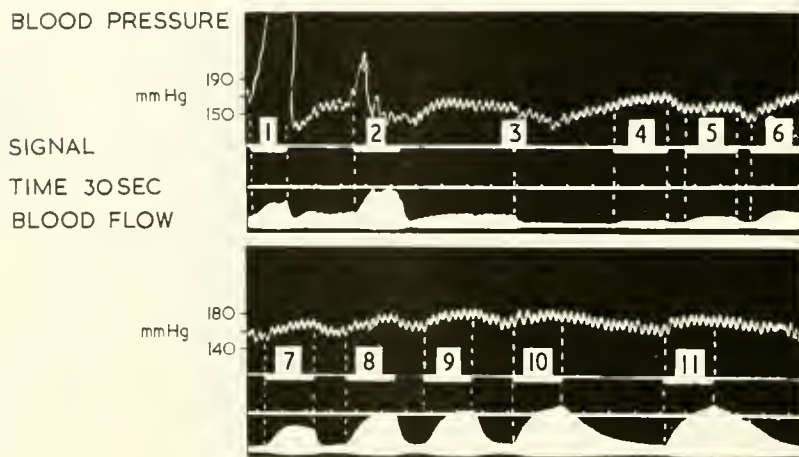


FIG. 11. Preparation used by Folkow to investigate the impulse frequency in sympathetic vasoconstrictor fibers. [After Folkow (90).]

below 7 or so per sec the blood flow returned rapidly to its initial value, but its restoration became more and more delayed after stimulations at progressively higher frequencies. Folkow then turned his attention to the venous outflow from the leg muscles of the opposite side of the cat, the side on which the abdominal sympathetic chain was still intact; maximal physiological stimulation of the vasoconstrictor fibers (only) was induced by clamping both carotid and vertebral arteries. The vagi had been cut. The possibility of adrenaline secretion had been eliminated and arterial inflow pressure into the leg was kept constant by tightening a screw clip on the abdominal aorta. The reduction in flow during carotid and vertebral occlusion and the rate of its restoration afterward were then compared with the reductions in flow and subsequent rates of restoration that had been obtained during and after electrical stimulation of the peripheral end of the cut abdominal sympathetic chain. The comparison showed that maximal physiological stimulation of the vasoconstrictors (by occlusion of the arterial supply to the head) caused changes in muscle blood flow closely resembling those recorded during and after electrical nerve stimulation at 6 to 8 per sec. Blood flow during stimulation at 6 to 8 per sec was reduced by 80 per cent of the maximal reduction recorded during maximum electrical stimulation at 16 per sec.

FIG. 12. Results obtained with the preparation seen in fig. 11 showing that maximum physiological frequency in vasoconstrictor fibers to the leg muscle is about 6–8 per sec. [After Folkow (90).] 1, 2, carotid occlusion; 3, sympathectomy; 4, 0.5 stim./sec.; 5, 1 stim./sec.; 6, 2 stim./sec.; 7, 4 stim./sec.; 8, 6 stim./sec.; 9, 10 stim./sec.; 10, 15 stim./sec.; 11, 20 stim./sec. For further details see text.



Sympathetic Vasodilator Nerves

Folkow & Uvnäs (102) noticed that after Dibenamine, stimulation of the abdominal sympathetic chain caused marked vasodilatation in the cat's hind limbs. The reason was sought in a later paper (103). What kind of fibers had they been stimulating? Were they true sympathetic fibers? To decide this they extirpated dorsal root ganglia L_1 to L_5 on one side and allowed 10 to 14 days for the sensory fibers to degenerate. However, this did not diminish the vasodilator response in the legs during stimulation of the abdominal sympathetic chain. From this and other elegant experiments they concluded that the increase in blood flow must be due to stimulation of none other than sympathetic vasodilator fibers. That being so they then investigated the whereabouts of this vasodilatation in the hind parts. Stimulation of the abdominal sympathetics did not increase flow in the saphenous vein draining the skin, on the other hand the flow from the vena cava draining skinned hind parts, with the paws tied off, did increase very greatly. They concluded that the increase must have been in the muscles. Other investigators had shown that the skeletal muscles of the dog are supplied by sympathetic vasodilator fibers (47).

CHEMICAL TRANSMISSION AT SYMPATHETIC VASODILATOR NERVE ENDINGS IN SKELETAL MUSCLE. These are cholinergic. Folkow *et al.* (96) showed this in cats given Dibenamine to block the action of sympathetic vasoconstrictor fibers. They noticed that the vasodilator response to stimulation of the abdominal sympathetic chain was much reduced by atropine. Atropine did not reduce the vasodilator action of adrenaline or of histamine. If the abdominal sympathetic vasodilator fibers were cholinergic, they argued, the vasodilatation should be potentiated after inactivation

of cholinesterase by eserine. It was difficult to test this because the combination of Dibenamine and eserine caused almost maximal vasodilatation in the hind legs. Positive results were obtained in only a few experiments. Nor could they test the effect of the venous effluent on the eserinated leech muscle because there were no leeches in Sweden. However the results of tests made with extracts of the venous effluent upon the cat's blood pressure and upon the frog's rectus muscle showed beyond any doubt that sympathetic vasodilator nerve stimulation did release acetylcholine. Folkow & Uvnäs (105) could find no evidence for the existence of adrenergic vasodilators to muscle vessels in the cat. In the dog too these vasodilator fibers are cholinergic (46).

ACTIVATION OF SYMPATHETIC VASODILATOR FIBERS TO SKELETAL MUSCLE BY HYPOTHALAMIC STIMULATION. Eliasson *et al.* (78) were the first to show that stimulation of the hypothalamus activated the sympathetic vasodilator fibers to muscle blood vessels. These fibers must have been solely responsible as the response was abolished by minute doses of atropine or by section of the abdominal sympathetic chains. Figures 13 and 14 show the preparation and a typical result. As hypothalamic stimulation caused constriction in the skin and intestines, tachycardia, constriction of the spleen, and dilatation of the pupils, they thought that activation of the vasodilator fibers to the skeletal muscles must be part of the reaction of a state of emergency in which a sudden increase in muscle blood flow is often needed for muscular activity. Further studies have since been made on the central connections of these fibers (2–4, 79, 139, 140).

SYMPATHETIC VASODILATOR FIBERS TO HUMAN SKELETAL MUSCLES. Observations on man suggest that these

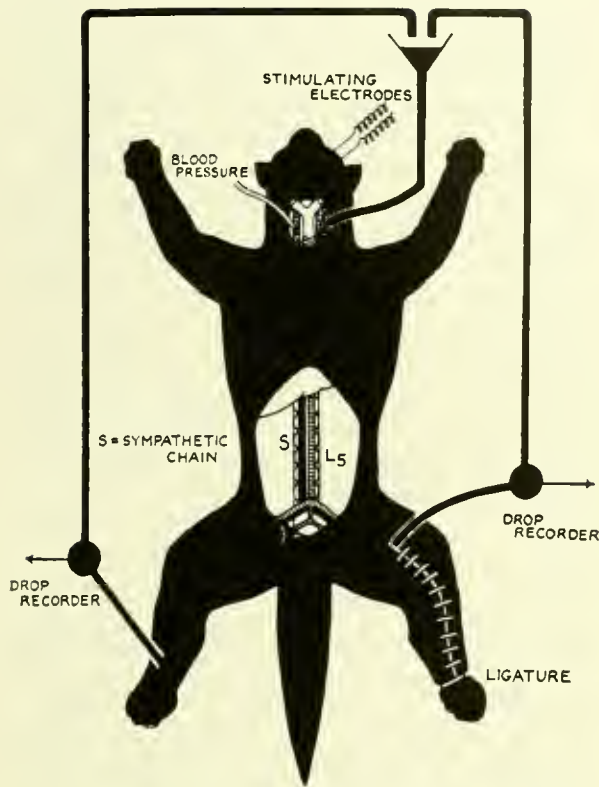


FIG. 13. Preparation used for investigating the effect of hypothalamic stimulation in the skin and skeletal muscle of the dog's hind limb. [After Eliasson *et al.* (78).]

fibers exist and are activated during fainting and emotional stress. During fainting, the vasovagal syndrome, induced experimentally by hemorrhage, the arterial blood pressure falls precipitously but blood flow in the forearm increases. There must be marked vasodilatation in the forearm (24). This vasodilatation is absent in sympathectomized forearms and is mediated by sympathetic fibers. It is probably in the skeletal muscles, although this has not yet been examined with the Hensel needle, or by observations of the changes in oxygen saturation of the blood draining from the deep forearm veins, or by inducing faints in subjects after arresting most of the circulation in the forearm skin by adrenaline electrophoresis. Is the vasodilatation due to inhibition of sympathetic vasoconstrictor tone or to activation of sympathetic vasodilator fibers? It is difficult to devise a satisfactory experiment to decide which is responsible. During the faint the average blood flow in six nerve-blocked forearms was less than that in six normally innervated forearms. Therefore it seems likely that vasodilator fibers were activated (22). However, in the cat simple inhibition of vaso-

constrictor tone causes fall in arterial blood pressure accompanied by increase in muscle blood flow (Folkow, personal communication).

It is worth noting that the vasodilatation in muscle in fainting is probably large enough to be mainly responsible for the fall in blood pressure and so for loss of consciousness (24).

Vasodilators to human muscle are probably activated in emotional stress. Wilkins and Eichna found that calf blood flow increased when a subject was given a mental arithmetic problem which took him about 15 sec to solve. They thought that this vasodilatation was mediated both by the sympathetic nerves and by adrenaline secretion (179). Others have studied the effect on forearm blood flow of harassing subjects with mental arithmetic problems for several minutes. They have shown with the Hensel needle that the vasodilatation is in the forearm muscles (44, 83, 111), and that the response is reduced, though not abolished by atropine, so that it is probably mediated to some extent by activity in vasodilator fibers (16, 42).

Blair *et al.* (37) frightened subjects by telling them

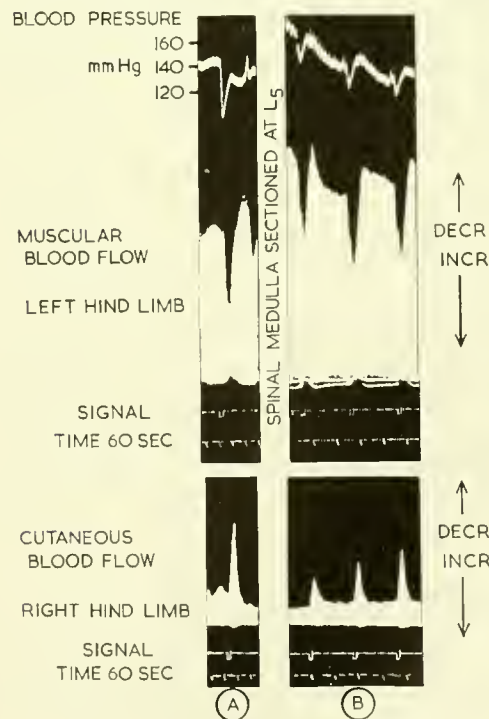


FIG. 14. Results obtained with the preparation shown in fig. 13. Stimulation of part of the hypothalamus caused vasodilatation in the skeletal muscles and vasoconstriction in skin of the hind limb. Section of the lumbar spinal cord did not abolish these effects which were mediated by the sympathetic chains.

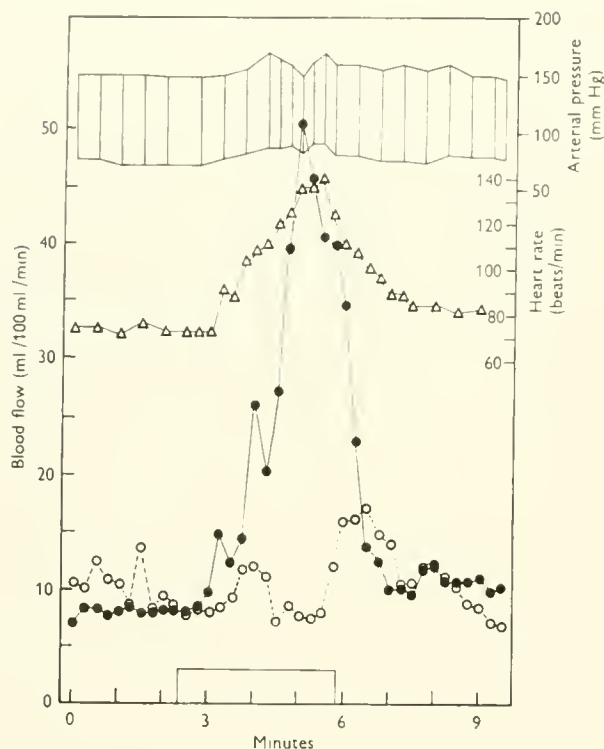


FIG. 15. Results showing that active cholinergic vasodilator nerves to human muscle contribute to the vasodilatation in the forearm muscles during stress. *Open circles:* hand blood flow. *Solid circles:* forearm blood flow. During the time represented by the rectangle it was suggested to the subject that he was suffering from severe blood loss. [Blair *et al.* (39).]

that they were suffering from severe blood loss. In one experiment, the result of which is illustrated in figure 15, forearm blood flow rose from 8 to 50 ml per min, while hand blood flow was not affected. In another subject oxygen saturation of blood draining from muscle rose from 20 to 65 per cent. In six subjects the vasodilator responses to a wide variety of stimuli were found to be reduced by atropinization of the forearm. They concluded that activation of cholinergic vasodilator nerves to human muscle contributed to the vasodilatation in the forearm muscles during stress.

Do Posterior Root Fibers Affect Muscle Blood Flow?

There is no important evidence of any efferent pathway via the posterior roots to animal or human muscle vessels. These fibers certainly play no part in the arterial baroreceptor reflex which is mediated solely by sympathetic vasoconstrictor fibers (101), and they play no part in hypothalamic vasodilatation which is mediated solely by sympathetic vasodilator

fibers (78). In man, too, sympathectomy of the limbs completely abolishes all known vascular responses of central origin.

There remains the question of whether or not axon reflexes from sensory endings in muscle influence the vessels. If so, then stimulation of the posterior roots should cause "antidromic" vasodilatation in muscle. Celander & Folkow (56) investigated the effect on paw flow and muscle flow of stimulation of the peripheral cut ends of L5-S2. There was marked vasodilatation in the paw but no effect on the circulation in muscle. Nor was there any change in the flow through muscle when the small C-fibers were selectively stimulated by heating the sciatic nerve. They concluded that axon reflexes in muscle were of very little significance.

Effect of the Temperature-Regulating Center on the Circulation in Muscle

It is well known that rise in body temperature releases sympathetic vasoconstrictor tone in the paws. However the temperature-regulating center has very little influence on the circulation in muscle. Folkow *et al.* (100) heated the cat's hypothalamus by diathermy and recorded marked cutaneous vasodilatation, but there was no change in the venous return from the skinned hind parts. In man, Edholm *et al.* (75) recorded marked increase in flow in the forearm during body heating, but this was absent in the opposite forearm in which the cutaneous circulation had previously been arrested by adrenaline electrophoresis. This has been confirmed by observations of muscle flow made with the Hensel needle (15) and by measurements of the oxygen saturation of blood obtained from veins draining muscle (165). Body heating which causes sweating and rise in mouth temperature does not increase blood flow in skeletal muscle.

Role of Sympathetic Fibers to Muscle in Exercise

Gaskell (108, 109) at first thought that vasodilator nerves were responsible for the vasodilatation in muscle in exercise, but later he realized that the action of metabolites was more important (107). There is strong evidence that the hyperemia of exercise is due to the action of a local mechanism which is triggered by the process of contraction. For example, Hilton (120) and others showed that the muscular contractions and vasodilatation elicited by motor nerve stimulation are both completely abolished by

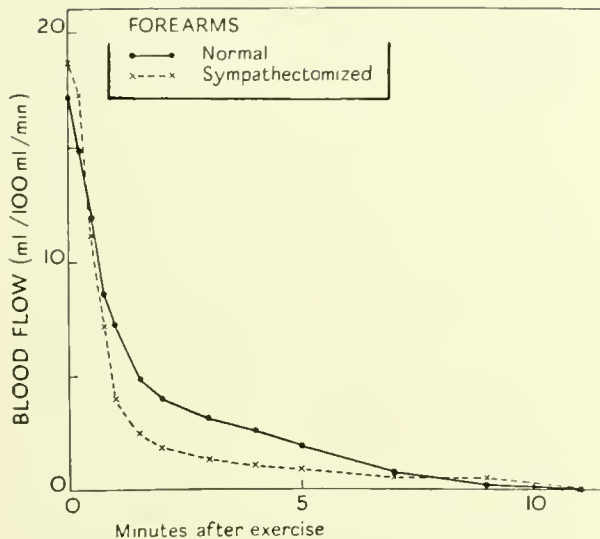


FIG. 16. Results showing vasodilatation in normal and sympathectomized muscle after exercise. Ordinate gives increase in blood flow above normal level. [After Grant (113).]

curare. Curare does not paralyze vasodilator nerve endings so that the vasodilatation must have been due to the contractile process. Muscles given atropine, and then stimulated, vasodilate quite normally in spite of cholinergic vasodilator nerve block (11, 106). Dogs are normally active after extirpation of both sympathetic chains (53) and human beings with sympathectomized limbs walk and cycle and take all forms of normal exercise. Before lumbar sympathectomy a policeman ran 380 yards in 65 and 61 sec; 99 days after sympathectomy he did it in 60 and 61.5 sec (H. Barcroft and J. S. Paddle, unpublished observation). Figure 16 shows that in a sympathectomized forearm the blood flow rose 19 ml per 100 ml per min after clenching a bar hard for 1 min, in a normal forearm the blood flow rose only 18 ml (113). Such findings show that the sympathetic vasodilators were not responsible for muscle vasodilatation in any of these activities.

However, there is no doubt that in exercise sympathetic impulse discharge to skeletal muscular system may alter. Blair *et al.* (41) recorded blood flow in both forearms and harassed a subject to do his best to exercise one of them in which voluntary movement had been paralyzed by a curare-like substance. The subject's strenuous efforts were accompanied by vasodilatation in both his forearms. As this was equal in the two sides, they concluded that the specific vasodilator fibers to a specific muscle group are not activated during activation of the motor nerves to the group in question.

In other experiments the circulatory changes in the forearm were recorded while subjects, who were recumbent, performed bicycling exercises with their legs. During these exercises arterial blood pressure rose and forearm blood flow decreased so that vascular resistance in the forearm increased. This vasoconstriction was still present when the cutaneous nerves were blocked but it was absent after deep nerve block. It was mediated by the sympathetic fibers to muscle vessels. Since it was not affected by previous atropinization of the forearm it must have been due to activation of the vasoconstrictor fibers.

There then is a paradox. The vasodilators were activated when the subject tried hard to exercise his paralyzed forearm, but it was the vasoconstrictors that were activated during the bicycling experiments. Can this be explained as follows? In the bicycling experiment the vasoconstriction was probably a manifestation of generalized vasoconstriction of the resistance and capacitance vessels, involving the splanchnic area too, and providing blood for the large increase in output necessary to supply the active legs. In this exercise the effect of activation of the vasodilator fibers may have been overpowered by much stronger activation of the constrictors. On the other hand, when an emotionally stressed subject begins exercise the combined actions of the vasodilator nerves and the local factor would be expected to cause more than usually rapid vasodilatation in his active muscles.

ACTION OF SYMPATHOMIMETIC SUBSTANCES

Noradrenaline

Given intra-arterially, in animals or man, noradrenaline constricts muscle vessels in all effective doses (27, 29, 55, 59, 94, 117, 178). Given intravenously in animals its constrictor action may be overcome by the rise in blood pressure; if this is prevented (59) or obviated (55) the muscle vessels constrict. In man, at the beginning of an intravenous noradrenaline infusion, there may be a transient vasodilatation, and after this the flow settles down at about the initial rate for the rest of the infusion period; reflex vasodilatation of sympathetic nervous origin usually masks noradrenaline's direct constrictor action (25, 178).

Adrenaline

The literature contains numerous references to the effect of adrenaline on the circulation in skeletal

muscle (see 116, 147). Many of the results are difficult to interpret. Artificial perfusion pumps, often used in these studies, must have damaged the blood and, because of the release of vasodilator substances, basal tone in the muscle vessels may be weakened (91). About the use of artificial pumps Folkow (91) says "The present experiments indicate that slight interference with the blood supply may damage the blood cells with release of substances that considerably depress the tone of the vascular smooth muscles and their reactions to different types of stimuli. The mere passage of normal arterial blood through a pump device of the type generally used in the perfusion experiments releases these substances in concentrations big enough to depress the vascular tone. The rougher the handling of the blood the bigger will their effects be . . . The substance (or substances) is contained in the blood cells, probably in the erythrocytes, and is rapidly destroyed while passing the lungs, even when present in big concentrations . . . It must be a very potent vasodilator agent, as the erythrocytes of only 0.5 mm³ blood contain amounts enough to elicit a well-defined vasodilatation . . . All these characteristics are typical also for ATP.

"It should be stressed, that most blood pump devices are very unsuitable for a study of the reactions of the blood vessels, as their vascular smooth muscles rapidly loose their tone and reactivity to most kinds of influences due to the fact that big amounts of vasodepressor agents are then released from the formed elements of the blood. . . ." These remarks apply to the cat (Folkow, personal communication).

Besides being observed during pump perfusion, the action of adrenaline was usually studied after the hormone had been given rapidly by single injection, so that there was not enough time for the resulting action on the vessels to reach a steady state.

Dale & Richards (63, 64), in two classic papers, showed that small doses of adrenaline cause vasodilatation in the denervated muscles of the cat's hind limb.

Clarke (57, 58) gave adrenaline by intra-arterial infusion. His records of the venous outflow from the skinned limb of the cat show that it had a biphasic effect—vasodilatation followed by vasoconstriction. The vasodilator effect has been attributed to liberation of acetylcholine (174, 175), but this has been denied. Celander (55) recorded the changes in venous outflow from the denervated muscle of the cat's hind leg. Close intra-arterial infusion of adrenaline at 0.04 μg per kg per min had no effect (fig. 17A);

0.07 μg per kg per min caused a large transient dilatation accompanied by a small sustained one lasting till the end of the infusion (fig. 17C); 0.13 μg per kg per min caused the initial transient vasodilatation followed, in this case, not by sustained vasodilatation but by sustained constriction (fig. 17B). Whether the initial transient vasodilatation was followed by small sustained vasodilatation or by sustained vasoconstriction was a matter of dosage. As to the explanation of this paradox Celander says: "It is hard to conceive that the direct effect of *l*-adrenaline on the smooth muscle cells of the muscular blood vessels at a low dosage should be relaxation while the same substance on the same substrate at a higher dosage would bring about a constriction. It seems more reasonable to assume that the dilator action of *l*-adrenaline is an 'indirect' one and that its disappearance at a higher dosage of *l*-adrenaline is related to the 'direct' constrictor action of *l*-adrenaline. In that case the dilatation would be due to the mobilization of a vasodilator factor released by *l*-adrenaline in the surrounding skeletal muscle cells with a secondary influence on the smooth muscles of the blood vessels." The author thought that the sustained vasodilatation was a phenomenon which should be looked upon more as a "metabolic" action of adrenaline than as a direct "motor" action. He also thought

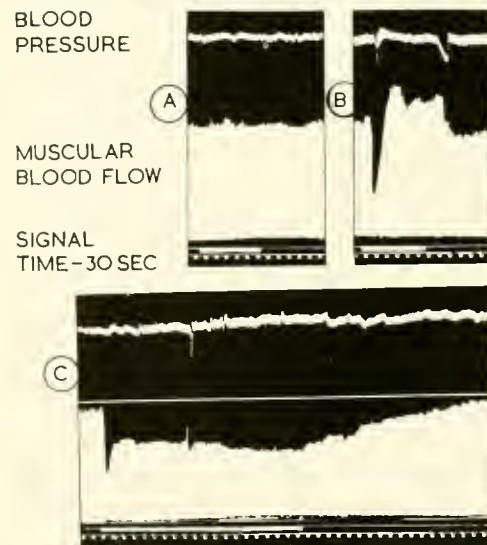


FIG. 17. Effects on muscular blood flow of *l*-adrenaline given intra-arterially. Perfusing blood pressure 120 mm Hg. Body weight 2.5 kg. A: I-A infusion *l*-adrenaline 0.04 $\mu\text{g}/\text{kg}/\text{min}$. B: I-A infusion *l*-adrenaline 0.13 $\mu\text{g}/\text{kg}/\text{min}$. C: I-A infusion *l*-adrenaline 0.07 $\mu\text{g}/\text{kg}/\text{min}$. For further details see text. [From Celander (55).]

that the "after-dilatation" seen after the larger infusions (fig. 17*B*) might well be due to the action of some carbohydrate metabolite diffusing slowly from the skeletal muscle cells. This substance was perhaps lactic acid as Lundholm (144) had suggested.

Celander (55) also recorded the changes in venous outflow during intravenous adrenaline infusions. Arterial pressure in the cat's legs was kept constant by adjusting a screw clip on the lower abdominal aorta. The general picture was the same—initial transient vasodilatation followed by smaller sustained vasodilatation or by constriction according to the infusion rate. There was one important difference. Far greater amounts of adrenaline—about five times as much—had to enter the leg before the sustained vasodilatation gave place to constriction. In the case of intravenous infusions the local constrictor action of adrenaline was believed to have been opposed by the vasodilator action of a substance liberated into the general circulation. Celander thought this substance was perhaps lactic acid from the other muscles.

Celander's (55) investigation also included the changes in venous outflow caused by unilateral splanchnic nerve stimulation. Here, too, arterial pressure in the leg was kept from rising by tightening a screw clip placed proximally. Stimulation at frequencies of 1 to 6 per sec (corresponding to bilateral splanchnic stimulation at 0.5–3/sec) caused sustained vasodilatation in the skeletal muscles. Further increase in the frequency was accompanied by progressively less vasodilatation. The results may have been complicated by liberation of substances from the liver; but they are interesting because it is via the splanchnic nerves that the suprarenal gland receives its natural stimulus.

The human experiments on the biphasic and other actions of adrenaline on muscle vessels are of particular interest. To quote Lewis (138), "It is perhaps impossible to measure the relevant quantities so precisely in man as in animals that are reduced by anaesthesia to perfect stillness and control. The disadvantage is offset, however, in other directions. It is the reaction in man himself of which we particularly require knowledge. Moreover, in human experiments the nutrient fluids bathing the limb are those natural to the limb and to the reaction, and this has not always been the case in animal experiments. Our observations are undertaken upon the unanaesthetised subject, the body as a whole is healthy and undisturbed, the general circulation is perfect, conditions rarely, if ever, realised in animal

experiment, and yet probably essential to an elucidation of the full truth where such a delicate reaction is concerned."

The subject is given a continuous infusion of saline into the brachial or femoral artery throughout the experiment. When appropriate the syringe containing the saline is replaced by another containing the same saline solution to which adrenaline has been added. The subject does not know whether syringes contain adrenaline or not. Thus when adrenaline is given, changes in forearm or calf blood flow can safely be attributed to the adrenaline itself; neither the saline nor emotional stress can be responsible (29). Soon after the beginning of an intra-arterial adrenaline infusion blood flow in the muscular part of the limb increases abruptly, reaching a peak in about 1 min. From the peak the flow subsides abruptly to a little above the initial level at which it remains for the rest of the infusion period. The vessels, as it were, "yawn"—they open wide and close. This initial transient vasodilatation occurs at the beginning of infusions at rates varying from about 0.001 to 2.0 μg per min. The biphasic pattern of the response is very striking (177). When the rate of the infusion is increased stepwise, each increase in rate is accompanied by its own transient initial vasodilatation (29). Intra-arterial infusion of very large amounts of adrenaline, far above the physiological range, causes sustained vasoconstriction.

As figure 18 shows, the initial biphasic transient dilatation is also the first response of the muscle vessels of man to infusions of adrenaline given by the intravenous route. The subsequent residual sustained vasodilatation is larger than that recorded during intra-arterial infusions (29, 74, 177). Thus in the forearm an intravenous infusion at 10 μg per min is accompanied by an initial fivefold increase in flow after which the rate subsides to about double the initial value for the remainder of the infusion period (5, 29, 178). That both the initial transient and the subsequent smaller sustained vasodilatation take place in the skeletal muscle has been shown by records taken with a Hensel needle implanted in the calf muscles (14, 26). This is seen in figure 19.

There is then a close resemblance between the action of adrenaline on the vessels of the skeletal muscle of man and of animals. The mechanism of the initial transient vasodilatation and of the later sustained one is plainly of great fundamental significance. It will be convenient to consider first the nature of the initial biphasic effect which is such a

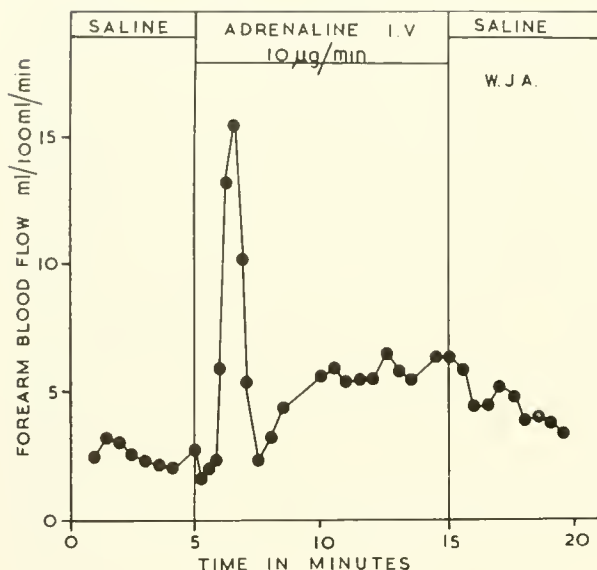


FIG. 18. Results show the effect of an intravenous infusion of adrenaline in man on forearm blood flow. The initial large transient and later smaller sustained vasodilatation are due to the action of adrenaline on the blood vessels in the skeletal muscles.

constant and conspicuous response of the vessels in the muscles of the calf and forearm.

During the initial vasodilatation blood flow increases about fivefold. The main resistance vessels, the arterioles and precapillary sphincters must be widely dilated. This is in accordance with microscopic observations made by Hartman & Walker (118) on the tibialis anticus of the cat. Small doses of adrenaline dilated arterioles, capillaries, and venules. In man this dilatation is not dependent on nervous connections. It occurs after nerve block, after sympathectomy, and in completely denervated limbs (29, 177). It must be due to the local action of adrenaline in the skeletal muscles. This might be a direct action on the plain muscle of the arterioles or a metabolic action due to products of carbohydrate metabolism released by the action of adrenaline on the skeletal muscle fibers. That the action of adrenaline is direct rather than metabolic is shown by the following observations. In the first place, the initial vasodilatation is not accompanied by any rise in venous blood lactate, which may even fall, so it is not likely that there is a rise in the concentration of any other

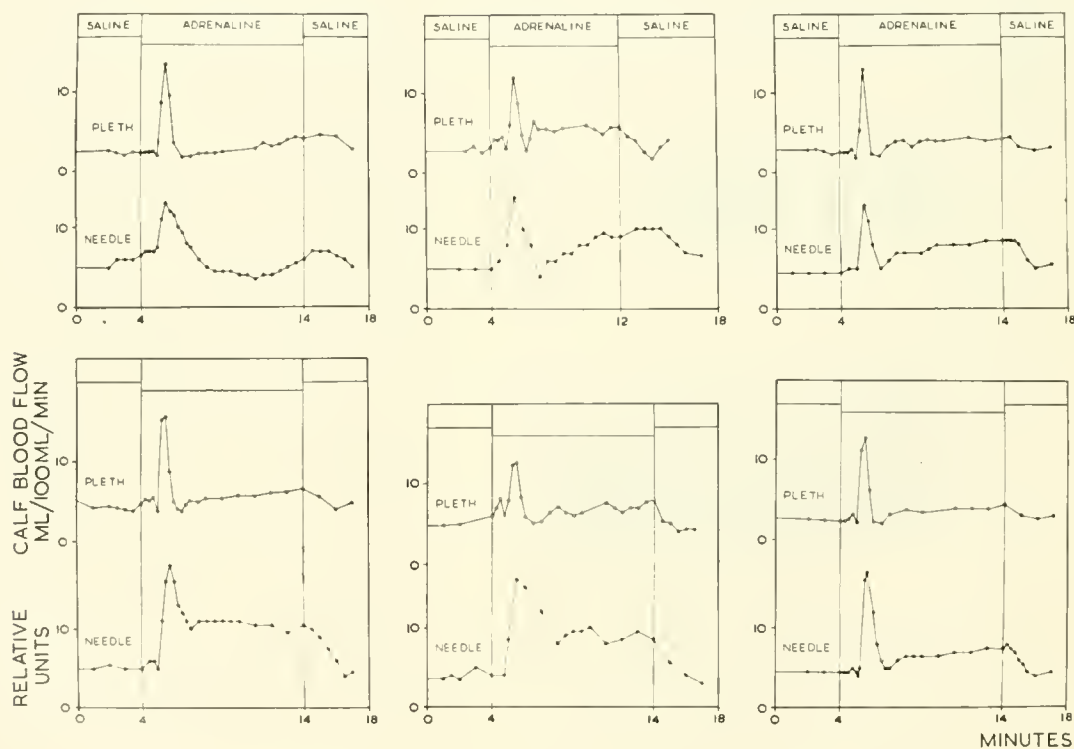


FIG. 19. Simultaneous records of the changes in blood flow in calf of the leg (plethysmograph) and in the muscles of the calf of the leg (Hensel needle) recorded in six experiments before, during, and after the intravenous infusion of adrenaline. [After Barcroft *et al.* (26).]

metabolite from the skeletal muscle fibers (17). Secondly, a perfectly normal initial vasodilatation has been recorded in a patient whose muscles, owing to an inborn error of metabolism, contained no phosphorylase, so that the vasodilatation was probably not due to any product of glycolysis (146, 170; also H. Barcroft and B. McArdle, unpublished observation). It seems reasonable to conclude that the initial vasodilatation is not due to the action of adrenaline on carbohydrate metabolism in the skeletal muscle fibers, and that it probably is due to the direct action of adrenaline on the plain muscle of the arteriolar walls.

Now we must consider the second part of the biphasic initial transient vasodilatation—the rapid return of the flow from the peak toward the resting level. Allwood & Ginsburg (7) and de la Lande & Whelan (136) have shown that this is due to a direct constrictor action of adrenaline on the muscle vessels. It can be partially or completely prevented by adrenergic blocking agents, as is shown in figure 20. That is to say adrenaline causes first vasodilatation in muscle almost immediately followed by vasoconstriction, which can be prevented by a blocking agent. The question now arises as to whether the vasodilator and vasoconstrictor phases of the initial transient vasodilatation take place in the same vascular bed, or is the opening of one set of vessels soon followed by the closing of another set in parallel? A little consideration of the extent of the changes in flow shows that the initial vasodilatation and the ensuing vasoconstriction must both take place in the same set of vessels. Suppose, as often happens, the flow before the beginning of the infusion was 3 ml per min. Then constriction in one bed could not reduce the flow by more than the preinfusion rate of 3 ml. In fact typical flows before, at, and after the initial transient vasodilatation may be 3, 15, 6 ml, respectively. That is, constriction may reduce the flow by 9 ml, i.e., by three times the total preinfusion rate. Plainly this could only happen if the vessels had first dilated so that they could be constricted to this extent.

It is well known that the action of adrenaline on a piece of smooth muscle can be biphasic (45). It is highly probable that the vasodilator and constrictor phases of the initial transient vasodilatation are both due to a direct biphasic action of adrenaline on the smooth muscle coat of the arterioles of the skeletal muscle vessels. This would be in accordance with the fact that vasodilatation invariably comes before constriction and that in any given infusion the sizes

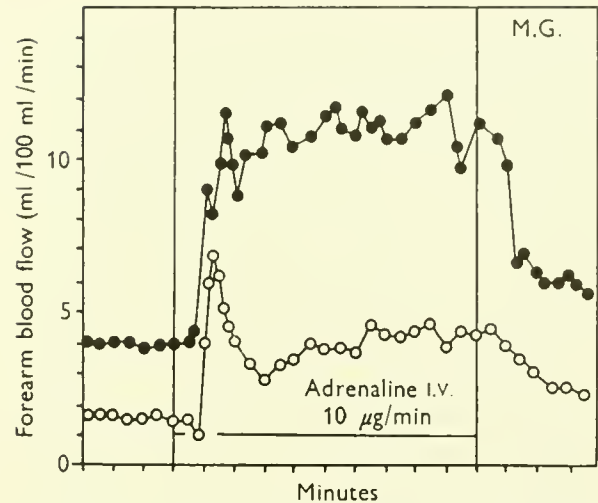


FIG. 20. Results showing that the rapid return of the forearm blood flow from the initial peak towards the resting rate during adrenaline infusions is due to a direct vasoconstrictor action on the muscle blood vessels. *Open circles*: before chlorpromazine. *Solid circles*: after chlorpromazine. [From de la Lande & Whelan (136).]

of the vasodilatation and vasoconstriction are usually equal. If the inhibitory and excitatory actions of adrenaline were to take place in different parts of the same vascular bed, i.e., in the arterioles and venules, it seems less likely vasodilatation would so closely relate to constriction in both time and extent. It is very difficult to imagine that the main resistance could shift from the arterioles to the venules. It is generally believed that adrenaline does constrict arterioles.

We must now turn to the smaller sustained vasodilatation that follows the large initial transient one. Similar sustained vasodilatation in muscle would be expected to accompany a continuous release of adrenaline from the adrenal glands. It will be recalled that Celander (55) observed sustained vasodilatation during intra-arterial adrenaline infusions and attributed it to the action of lactic acid liberated by the metabolic action of adrenaline in the skeletal muscle fibers. Intra-arterial infusions of adrenaline in man are also accompanied by local release of lactic acid (6) and the small sustained vasodilatation in such infusions may be due to an indirect metabolic action of adrenaline on the skeletal muscle fibers. The evidence so far available shows that the sustained vasodilatation in man is rather larger during intravenous than during intra-arterial infusions (29, 74, 177). Celander (55) found the same in animals and thought that it was because during intravenous infusions the

muscle vessels were dilated not only by locally liberated lactic acid but also by lactic acid liberated from other muscles into the general circulation. Many experiments have been done on man to try to explain why the sustained vasodilatation is larger during intravenous infusions than it is during intra-arterial ones. It is not due to rise in arterial blood pressure, nervous reflexes (29, 177), histamine formation (153), or secretion of the pituitary (135). It is probably explained by the fact that during intravenous infusions the concentration of adrenaline remains constant independently of the rate of flow, whereas the concentration varies reciprocally with the rate of flow during intra-arterial infusions. The large sustained vasodilatation typical of an intravenous adrenaline infusion can be obtained too during an intra-arterial infusion, if the rate of infusion of the hormone is gradually increased so as to keep its concentration constant (143a).

Effect of Adrenaline on the Circulation in Skeletal Muscle During Exercise

It is often stated that adrenaline dilates muscle blood vessels in exercise. So far as I am aware there is no evidence that it actually does so. The idea is often accepted as part of Cannon's Emergency Theory of the function of the autonomic nervous system. So far as I can find, Cannon himself never suggested it (49-52). On the other hand, why are the plain muscle coats of the arteries in the skeletal muscles specialized so that they are rapidly dilated by adrenaline? Is this of any teleological value in the cat or man? Or was it of value in some extinct ancestor? Or is it just a coincidence?

A few minutes after the beginning of long-lasting repetitive stimulation of the motor nerve to the dog's gastrocnemius, the oxygen saturation of the venous blood draining from the muscle sinks to its lowest point to rise again later. This is because of delay in the rate of opening of the vessels. If in the exercising animal adrenaline secretion helped to open the vessels, the provision of oxygen and disposal of waste products would be facilitated.

When exercise begins the blood pressure rises, sympathetic impulse discharge increases, and metabolite concentration in the muscle mounts up. It would be very difficult to devise an experiment in the cat, dog, or human to determine the extent to which the initial dilatation of the muscle vessels was in fact due to the action of adrenaline.

In man, emotional stress at the beginning of exer-

cise may be accompanied by adrenaline secretion (16). This would be expected to cause an initial transient vasodilatation throughout the entire skeletal muscular system. In active muscles the vessels would be rapidly dilated and the constrictor phase of the initial biphasic response might well be blocked by the action of the mounting concentration of metabolites. In animal experiments the constrictor action of adrenaline is blocked if muscles are active (150). In other muscles which were not contracting the constrictor part of the biphasic response would manifestly be of use as it would prevent useless and wasteful hyperemia. To quote from August Krogh (134), "Speculations such as these, though admittedly loose, are sometimes very useful. Sooner or later an opportunity offers of putting them to the test. It is, of course, very gratifying to find them confirmed, but generally they are even more useful when they turn out to be wrong, because, in that case, they serve to discover at what point the reasoning went astray and to guide it back into a channel which may possibly lead it onward. The problems of physiology are so complicated that, to put it tersely, one cannot expect to be able to reason correctly from the facts for more than 5 min at a stretch."

Apart from the beginning of exercise is the question of the action of adrenaline on the vessels later on (sustained vasodilator action). It is known that adrenaline continues to be secreted in severe exercise in man (82), but because of the very strong action of metabolites its effect on the vessels would be expected to be negligible. This is in accordance with the results of experiments. In dogs, Cannon *et al.* (49) found that the amounts of work that dogs could do to exhaustion on a treadmill was neither prolonged by previous injection of adrenaline nor shortened by previous adrenalectomy. In man Dornhorst & Whelan (68) found that the postexercise "blood debt" was not diminished when the exercise was performed during an infusion of adrenaline.

REACTIVE HYPEREMIA

Reactive hyperemia can be induced in skeletal muscle vessels. Hilton (120) recorded it in the cat's isolated gastrocnemius. Following temporary arrest of the circulation through this muscle, achieved by clamping the artery for 30 sec, the increase in blood flow was as great as that recorded after 30 sec of maximal tetanic contraction, but after ischemia the flow subsided more quickly. Folkow & Löfving (97)

found that temporary occlusion of the circulation through the cat's hind limb (paw tied off) was followed by reactive hyperemia. As the condition of the animal deteriorated, basal tone diminished and reactivity of the vessels decreased. Reactive hyperemia in skeletal muscles is soon lost when they are perfused with saline.

It is generally agreed that reactive hyperemia takes place independently of nervous connections. Bayliss (35) thought that the relaxation of the vessels during reactive hyperemia was due to lengthening of the plain muscle because, during the period of arrested circulation, the fibers were no longer subjected to the stimulus of stretch. Lewis (138) denied this because reactive hyperemia followed circulatory arrest by venous occlusion, during which the smooth muscle of the arterial walls was still distended by the arterial blood pressure. He did numerous experiments leading him to the conclusion that the response was due to the action of a histamine-like vasodilator substance the concentration of which, in the tissue fluids, increased during the ischemic period. Folkow *et al.* (95) and Emmelin & Emmelin (86) found that reactive hyperemia occurred quite normally in the limbs of animals in which the action of injected histamine had been completely blocked by antihistaminics. Therefore, they concluded that the response was probably not due to the action of a histamine-like substance. Guyton *et al.* (62) showed that reactive hyperemia cannot be due to the action of accumulated CO_2 . Ventilating dogs with 20 per cent CO_2 was not accompanied by any vasodilatation in the legs. On the other hand, reduction of the oxygen saturation of the blood to 30 per cent doubled the rate of the blood flow. Guyton *et al.* thought that oxygen deficiency might well be one of the causes of reactive hyperemia.

Most studies of reactive hyperemia in muscle in man have been made in the forearm or calf using venous occlusion plethysmography. However, one must always remember that the blood flows recorded by this method are not those in the skeletal muscle only, but include also the blood flow through the skin.

In man as in animals (120), the longer the period of arrest lasts the greater is the subsequent hyperemia in the forearm (158); the increase is mainly in the duration of high flows, the peak value being relatively little increased. Reduction of the arterial pressure during the period of arrest and of the stimulus of stretch may be partly responsible for the loss of vascular tone (156). Exposing the forearm to sub-

atmospheric pressure and thus "packing" it with blood before arresting the circulation lessens the fall of intravascular pressure during the period of occlusion. As in animals, so in the human forearm, antihistamines, such as tripeleminamine, mepyramine, and antazoline when introduced into the brachial artery do not diminish the reactive hyperemia that follows 3 min of circulatory arrest, although they completely abolish the increase in flow brought about by the intra-arterial injection of histamine (71).

Apart from histamine, various chemical causes, such as anoxia, have been suggested to explain reactivity in man. Lewis (138) says, "It is manifest that neither deficiency of oxygen nor an accumulation of carbon dioxide or other weak acid in the blood that is within the vessels can possibly form the direct stimulus; were that so the reaction would always be fleeting, the blood being at once replaced by the flood of the reactive hyperaemia." Certainly the vessels would be filled with fresh blood almost instantly, but does it follow that the reaction would be fleeting? After sudden removal of the stimulus how fast in fact would the vessels contract? Some kinds of plain muscle respond to stimulation rather slowly. Further experiments are needed on this important point. McNeill (148) showed that during the second minute of a reactive hyperemia in the forearm the oxygen saturation of the venous blood in the antecubital vein may rise transiently to well above the resting value. The effect is seen in figure 21. The reason for this transient rise in venous oxygen saturation, as McNeill showed, was that oxygen consumption returned to the resting level more promptly than did the blood flow; this corresponded to a transient decrease in utilization. Return of the blood flow to the pre-occlusion level may have lagged behind restoration of the circulation *a*) because of the presence of a nonoxidizable metabolite, or *b*) because the vessels simply could not contract fast enough to keep pace with the rapid fall of the concentration of some oxidizable vasodilator metabolite. Further work is necessary on this topic.

Dornhorst & Whelan (68) showed that, after a short period of arrest of the circulation in the calf, the rate at which the blood flow during the subsequent reactive hyperemia returns to initial levels is exponential; i.e., a straight line is obtained when log flow is plotted against time (compare fig. 24*B*). The significance of this fact is not clear. In other experiments, using a pressure plethysmograph, they studied the effect on reactive hyperemia of reduction of the

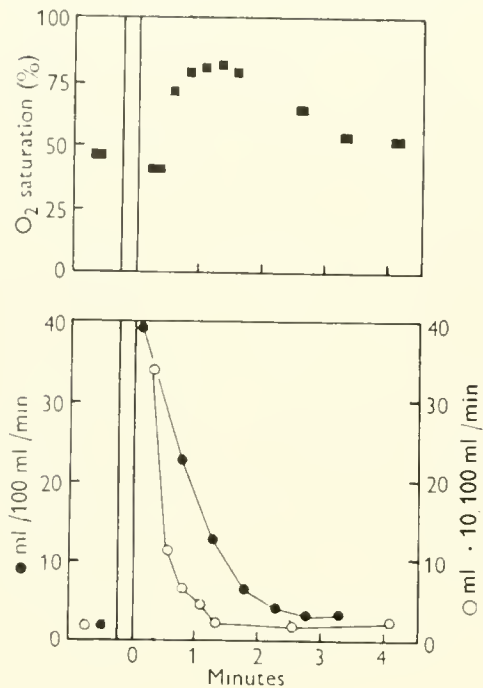


FIG. 21. Results showing that after circulatory arrest (vertical lines) the oxygen saturation in the venous blood rises to above the initial value. Oxygen consumption (open circles) returns to the resting level more quickly than the blood flow (filled circles). [From McNeil (148).]

arterial pressure. The resting rate of flow, post-ischemic peak and "area under curve" or "blood debt" were all much reduced, but this was not so for the exponential rate of restoration of the flow. They concluded that the flow could not depend on the local concentration of some metabolite, the removal of which depended critically on the rate of the blood flow. They say "the facts were compatible with the concept of a metabolite diffusing out of the tissues with a concentration gradient which effectively limits its rate of removal when the blood flow is above some small value, or of a metabolite oxidized at a rate dependent on its concentration and independent of the local oxygen tension when this exceeds some low figure." The significance of this finding is not yet known. Another relevant experiment was performed by Blair *et al.* (41). They studied the blood flow in the forearm after 5 min circulatory arrest. Coincident with the release of the circulation the brachial artery was compressed digitally for 5 min to prevent the blood flow from rising above the resting level. Release of the artery was not followed by any reactive hyperemia. They concluded that it was not necessary to have an increase in blood flow after circulatory arrest to "repay" the "debt" in-

curred during this procedure. It would be interesting to compare the oxygen debt incurred during the circulatory arrest with the subsequent oxygen repayment. So far as I am aware this has not been done, because of technical difficulty. [However, see (180).]

It is certainly worth recalling that reactive hyperemia in totally denervated forearms is just as great as in normal ones (72). Indeed, owing to the withering of the muscles the response per 100 ml is far greater in the denervated forearm. Can reactive hyperemia be due to ischemia of the plain muscle of the arterial tree?

EXERCISE HYPEREMIA

Active muscles must get oxygen from the air. To this end total ventilation increases, heart rate is speeded up, and muscle blood vessels dilate. We still do not know for certain the mechanism of any of these responses. The hyperpnea that we can see and the tachycardia that we can feel and record have attracted more attention than the deeply hidden dilatation of the muscle vessels. We still seem a long way from understanding the cause of the hyperemia of exercise. I recall some sentences of my father's. "Let us then jot down such information as is forthcoming in the hope that the points at issue may be taken up one by one by future workers, and that one day systematic work may be done on the subject. I say 'jot down' rather than 'put together' because to make any sort of story from such unsatisfactory material would be quite unwarrantable" (30).

Let us first "jot down" some points about the hypothesis that exercise hyperemia is caused by anoxia of the vascular tree. It is certainly worth noting that the rate at which muscle blood vessels open may be as fast after simple arrest of the circulation as during exercise. Eichna & Wilkins (77) found that the peak forearm flow after 5 min of simple circulatory arrest was as large as that after 5 min combined circulatory arrest and rhythmic exercise. Dornhorst & Whelan (68) recorded a peak flow of about 20 ml per 100 ml calf per min after 2 min ischemia; after 2 min rhythmic exercise the same post-exercise peak flow was recorded. Hilton (120) noted that the flow from the cat's gastrocnemius after 30 sec ischemia was the same as that after 30 sec exercise. True, the mechanisms of ischemia and exercise are not really comparable, but further work is necessary to see if ischemia opens the vessels as fast alone as when combined with exercise. If so, we must ask

whether the smooth muscles of the arterial tree relax simply because their oxygen is taken away by the active skeletal muscle fibers.

The experiments of Kramer and his colleagues (131-133, 160) have helped a great deal to establish the effect of exercise on the circulation and metabolism of muscle. The dog's gastrocnemius muscle was stimulated indirectly via its nerve. The rate of its venous outflow was recorded continuously by an optical method in milliliters per minute as also were the arterial blood pressure and the oxygen saturations of both arterial and venous blood; in some experiments blood lactate was estimated. From these, the relations between work done, blood flow, oxygen consumption, and lactate output were calculated. Figure 22 is from an experiment of Kramer's in which the sciatic nerve was stimulated maximally at 310 impulses per sec for 1 sec every alternate sec. The findings are relevant:

1) At the beginning of exercise venous blood oxygen tension fell abruptly to reach a "low" after about 1 min. Blood flow rose exponentially to reach a steady value in about 1 min. If the resting vessels were opened wide by acetylcholine then oxygen usage jumped up to the steady state as soon as the exercise began.

These facts may be interpreted as follows. As soon as exercise begins there is an immediate demand for oxygen, the supply of blood being quite inadequate, tissue oxygen tension falls to a very low level. This is reflected in the low oxygen saturation of the venous blood, and possibly also in the gradual relaxation of the plain muscle of the arterial tree. As vasodilatation proceeds and oxygen supply improves venous oxygen saturation rises somewhat.

2) During the steady state, blood flow, work done, and rate of oxygen consumption are linearly related. This is seen in figure 23. During submaximal exercises the muscle gets all the oxygen it wants (or almost). Opening the vessels still more with acetylcholine does not increase the oxygen consumption. It is not clear from these experiments whether the blood flow was linearly related to the decrease in venous blood oxygen tension. It seems very significant indeed that the rate of the blood flow is linearly related to the rate of oxygen consumption. Further work is needed to see how it is related to tissue oxygen tension.

3) Immediately after moderate exercise extra oxygen usage stops in a muscle the vessels of which are opened maximally with acetylcholine. When the circulation is normal, oxygen consumption and blood flow rapidly subside exponentially, oxygen consump-

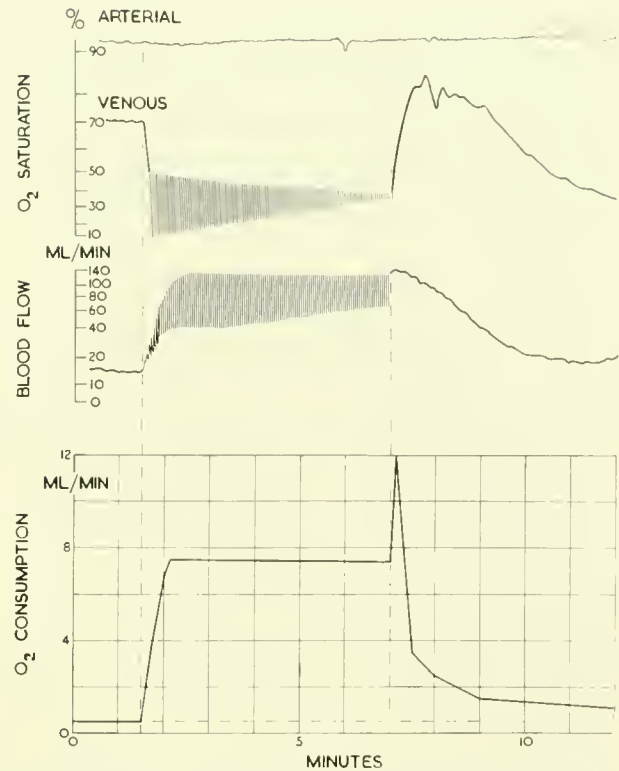


FIG. 22. Results obtained by Kramer and his colleagues. *Top:* records from which blood flow, oxygen saturation, and oxygen consumption were obtained. Rhythmic stimulation between the vertical lines. Note the remarkable rise in the venous oxygen saturation after the end of exercise. *Bottom:* results calculated from records like those shown above. [After Kramer *et al.* (132).]

tion falling a little more rapidly than blood flow. The behavior of the venous O₂ saturation is interesting. Immediately after exercise stops, it rises transiently to a peak and then subsides again to a low level from which it recovers only very slowly. The reason for the immediate postexercise peak may be as follows. The demand for oxygen being soon satisfied, the arterial tree is no longer anoxic and its plain muscle starts to contract. But the rate of contraction cannot keep pace with the fall off in demand for O₂. Hence O₂ saturation rises. It is not clear why, later on, the postexercise venous blood oxygen saturation subsides from the peak to a level almost as low as in exercise, and from which recovery to the pre-exercise level takes place only very gradually. Since at this time the rate of the blood flow is decreasing, it is plain that blood flow cannot be inversely related to venous blood oxygen tension. To be able to explain this odd finding would be to gain much insight into the mechanism of exercise hyperemia.

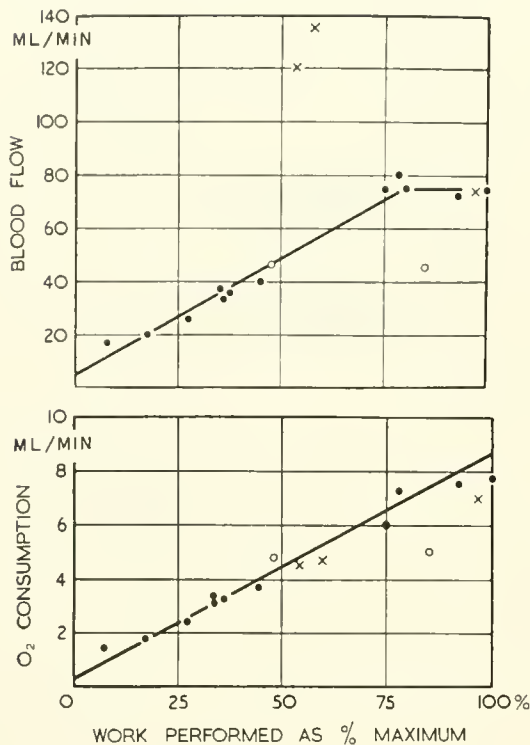


FIG. 23. Results showing that blood flow and oxygen consumption in the dog's gastrocnemius muscle were proportional to the work done during rhythmic contraction. [From Kramer *et al.* (132).]

So much for Kramer's experiments. It is worth recalling that Barger *et al.* (31) in their experiments on the regulation of the circulation in exercise in the normal dog also concluded, though from less direct evidence, that muscle blood flow and oxygen consumption were directly related.

It is worth noting that in hyperthyroid subjects the postexercise blood flow following a standard exercise is much increased (1). Here again an explanation might take us to the very center of the mechanism of exercise hyperemia.

But now we must "jot down" some results which make it difficult to picture a relationship between tissue oxygen tension and blood flow. Let us begin with experiments by Dornhorst & Whelan (68). They studied the effect of reduction of femoral arterial blood pressure on postexercise hyperemia in the calf muscles. The effective arterial pressure could be halved by means of a pressure plethysmograph. Figure 24 shows a typical result. After the arterial pressure was reduced by one-half, the postexercise hyperemia flows and "blood debt" were lowered but the hyperemia was not prolonged. The changes in the peripheral vascular resistance of the calf were

exactly similar to those found in the limb with normal blood pressure. Thus, if postexercise hyperemia depended on the local concentration of a metabolite, its removal or destruction could not depend on the rate of blood flow nor could its oxidation depend upon local oxygen tension. They concluded that for postexercise hyperemia, as for reactive hyperemia (see above), the vasodilatation could be due to an intracellular metabolite the removal of which from the tissue of the vessel wall is limited more critically by its diffusion gradient than by the rate of blood flow through the vessel lumen. Such a metabolite, they suggested, would be deactivated primarily by intracellular oxidation.

Holling & Verel (125) studied the effect of lowering the effective arterial pressure on the forearm blood flow. Arterial pressure was lowered by elevating the forearm. There was a linear relation between pressure and flow. Peripheral vascular resistance did not change. Compensation for reduction of perfusion pressure by vasodilatation did not occur. Oxygen tension in the elevated forearm was reduced as shown by the polarograph, but oxygen uptake was unaltered because of increased utilization. Their findings did not support the concept that metabolism of resting muscle played a prominent role in the regulation of its blood flow. In line with this, Blair *et al.* (40) showed that compression of the brachial artery for 5 min beginning at the end of 1 min rhythmic exercise of the forearm muscles altogether abolished postcontraction hyperemia. They concluded that it was not necessary to have an increase in blood flow after exercise to "repay" the "debt" incurred in exercise. This agrees with their observations following postocclusive (reactive) hyperemia (see above). However, by supplying the tissues with an excess of blood, postexercise hyperemia does return the tissues to the resting state more quickly than does the resting flow.

If oxygen lack of the arterial tree opens the vessels in exercise, then asphyxiating skeletal muscle should cause hyperemia. Bayliss (34), however, found that the blood flow through the denervated hind limb did not alter when the arterial blood was made asphyxial. Verzar (176) studied the effect of ventilating the cat with 8 to 10 per cent oxygen on the gaseous metabolism of the gastrocnemius muscle. Partial asphyxia of the muscle greatly reduced its rate of oxygen consumption but had no effect on the rate of the blood flow. The venous blood seldom became less than 30 per cent saturated with oxygen, nevertheless tissue oxygen tension in regions farthest

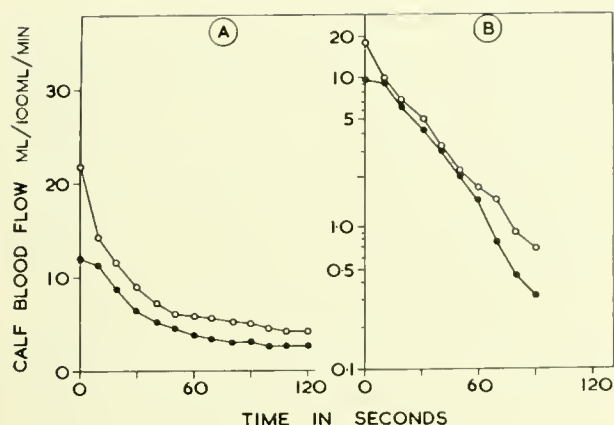


FIG. 24. Results showing that reduction of the arterial blood pressure did not affect the resistance changes in the muscle vessels of the calf of the leg after exercise. *Solid circles*: average of 12 runs in six subjects with pressure in plethysmograph raised 67 cm H₂O. *Open circles*: average of 12 control runs on the same subjects. *A*: simple scale; *B*: semilogarithmic scale. [From Dornhorst & Whelan (68).]

from capillaries could not have been far from zero. Others have found that venous blood from exercising muscles seldom contains less than 6 vol per cent oxygen (12, 31), and that muscle oxygen tension may be very low. For example, during tetanic stimulation of the cat's soleus oxygen saturation of the myoglobin falls from 90 to 50 per cent (152). Roughton has kindly told me that this corresponds to a fall in muscle oxygen tension of from about 40 to 5 mm Hg (F. J. W. Roughton, personal communication). Ehrlich (76) too, who measured the reduction of alizarin blue, found that muscles reduce very actively.

But what about the effect of really low arterial blood oxygen tensions on muscle flow? The trouble is that these kill the heart. It is true that Fleisch *et al.* (86), who perfused hind legs with blood artificially ventilated with 3 per cent oxygen, did not find much dilator effect. But their preparation had lost basal tone and was probably widely dilated before the effect of rarefied oxygen was tested. Because of the damage done to the blood of the cat by pumps (91) the experimenter who wishes to test the effect on muscle blood flow of complete reduction of the blood is faced with a very awkward technical problem. In dogs Guyton *et al.* (62) recorded some vasodilatation in the hind legs when the oxygen tension of the blood perfusing them was reduced to 30 per cent. We do badly need a study of the effect on muscle blood flow and gaseous metabolism of progressive reduction in O₂ tension of the arterial inflow right down as

far as zero. It will be recalled that Hilton & Eicholtz (124) found that ventilating the animal with N₂ was accompanied by a large increase in coronary blood flow. Results have not yet appeared on the effect of ventilating the animal with N₂ on the hyperemia of exercise, nor on the effect on the hyperemia of exercise of reducing arterial oxygen tension down to zero.

So much for oxygen lack. It was Gaskell's (107) idea that muscle blood vessels were opened by vasodilator metabolites liberated from the skeletal muscle fibers. It was he who first painted the arteries of the frog's mylohyoid with 1:10,000 lactic acid and observed the vasodilatation. However, lactic acid is probably not responsible for exercise hyperemia. Exercise is accompanied by the usual hyperemia in muscles that have been poisoned with moniodoacetic acid to prevent the formation of any lactic acid (112, 162). Exercise is accompanied by hyperemia in patients whose muscles, owing to congenital absence of phosphorylase, are unable to form lactic acid (146, 170). And there are awkward differences between blood flow and lactic acid time relations (133).

Fleisch & Sibul (85) found that neutral lactate had no dilator effect. That of injected lactic acid they thought to be due to its pH. Other substances which caused vasodilatation in concentrations of 1₆₀ to 1₃₀₀ ml per ml blood were methylglyoxal, Na-pyruvic acid, acetaldehyde, acetates, sodium acetoacetate, salts of fatty acids, and adenosine phosphate. Their actions were additive. Fleisch & Weger (88) investigated the action of fructose 1,6-diphosphate, dihydroxyacetone phosphate, phosphoglyceric acid, phosphopyruvic acid, phosphoglycerol, and creatine phosphate on the blood vessels of the cat's hind leg. All were inactive or weakly dilator. However, their results were not of much quantitative value because they used pump perfusion and worked with a preparation that had lost basal tone.

Gaskell (107) had suggested that CO₂ might be a factor and while Bayliss (35) showed that it had a vasodilator action Krogh (134), Fleisch (86) and others have shown that its effect is too weak to be of much significance.

Fleisch & Sibul (85) thought that the additive effect of carbohydrate metabolites might be considerable because of their reduction of the pH. But Gollwitzer-Meier's (112) determinations of the pH changes in the venous effluent of the exercising gastrocnemius of the dog did not support this hypoth-

esis. Moreover, as we have seen, exercise hyperemia occurs in muscles poisoned with moniodoacetic acid although their pH probably increases (112).

All workers are agreed as to the great vasodilator power of ATP and its related compounds in animals (88, 162, 171) and man (70). And several have suggested that it is concerned with exercise hyperemia. In fact the amount of ATP in muscle is probably reduced in exercise because of conversion to ADP. As we have seen the rate of the blood flow in muscle closely parallels the rate of its oxygen usage. But so far as I know there is no relation between muscle O_2 consumption and the rate at which ATP or ADP leaks out of the muscle fiber.

Dawes (65) suggested that potassium might be partly responsible for the hyperemia of exercise. This was based on the finding that intra-arterial injection of 5000 μg of potassium into the pump-perfused muscles of the dog's hind legs caused some vasodilatation. Once more attention is being focused on potassium. Kjellmar (130) found that postcontraction hyperemia in the cat's gastrocnemius muscle was accompanied by a rise in the potassium concentration in the venous effluent. Intra-arterial infusions of small amounts of potassium caused vasodilatation. But, and this is important, infusions of amounts far bigger than those found during exercise cause constriction. Tetanus of the cat's muscle during the potassium-induced constrictor phase was no longer followed by hyperemia, although injected vasodilator agents induced vasodilator responses. This suggests that the hyperemia of exercise may be at least partly due to the action of potassium ions. I do not know whether the rate at which K leaves the skeletal muscle fibers is related to their rate of oxygen consumption. We have seen how closely blood flow is related to oxygen consumption and to the work done.

Anrep and others (8, 9, 11) found that blood from active muscles contained histamine and that during contraction the amount of histamine in muscle diminished. Fleisch & Weger (87) repeated their experiments and concluded that the loss of histamine was due to the fact that the condition of the animals had deteriorated. In man, active muscles do not release a vasodilator substance, or if they do it does not survive a single passage through the lungs. The performance of leg exercise is not accompanied by any change in the vascular resistance of the nerve-blocked forearm (42).

Bradykinin has recently come very much to the

fore. Hilton (123) has shown that it is not implicated in the mechanism of exercise hyperemia.

In exercise muscle blood flow may increase tenfold. Peripheral vascular resistance in the muscle must have fallen to one-tenth of its normal value and the principal resistance vessels, usually considered to be the arterioles, must be widely dilated. This dilatation results from the action of metabolites produced either in the arterial tree itself or in the surrounding skeletal muscle fibers or in both. The question arises, if metabolites from the skeletal muscle fibers are involved, by what mechanism do they cause relaxation of the multilayered arteriolar plain muscle coat? The following points seem relevant:

1) It is not hard to imagine that vasodilator metabolites from the tissue fluids could quickly diffuse through the arteriolar walls. A good example of diffusion through thick tissues is that of a dental anesthetic, which in a short time seeps from the subcutaneous tissue of the gum through the maxillary bone into the tooth socket. Diffusion of metabolites through minute arterioles might well be very rapid indeed.

2) Schretzenmayr (172) made the curious discovery that contractions of the skeletal muscles in the lower part of the cat's leg are followed by increase in the diameter of the femoral artery in the inguinal region. Figure 25 illustrates this. Since this increase in diameter was not abolished by denervation, but was by painting the vessels with phenol, he thought that it must be an axon reflex from the active muscles to the arterial walls. Fleisch (84) confirmed this in the dog and showed that intra-arterial injections of acetic acid, of various intermediary products of

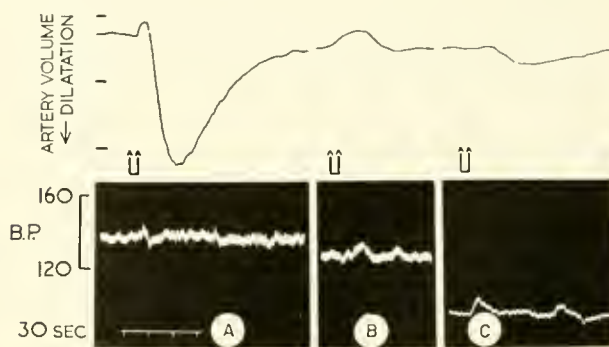


FIG. 25. Exercise of the leg muscles by stimulation of the sciatic nerve (A, between the arrows) caused dilatation of the femoral artery proximal to the muscle. After curare neither stimulation of the sciatic (B) nor of the muscle (C) had any effect on the diameter of the femoral artery. [From Hilton (122).]

muscle metabolism, of histamine and especially of acetylcholine all were followed by widening of the femoral artery.

Hilton (121, 122) compared the effects of a variety of drugs and procedures on postcontraction hyperemia and on the postcontraction dilatation of the femoral artery. The actions of drugs on these two processes resembled each so closely as to suggest strongly that they had a common mechanism. He noted also that the dilator response traveled slowly along the wall of the artery at about 10 cm per sec. Intra-arterial injections into the muscle of acetylcholine, histamine, bradykinin, and nicotine were all followed by intra- and extramuscular arterial vasodilatation. However

intra-arterial injection of ATP causes only intramuscular vasodilatation; he did not think that ATP could be concerned with the dilator response which accompanies muscular contraction (125).

3) D'Silva & Fouché (69) found that shunting the blood from the artery to the vein causes widening of the artery proximally. They think that the dilatation of the artery in exercise may not be due to metabolites but to a change in the rate of flow.

4) It seems important to bear in mind that muscle blood flow, work done, and oxygen consumption are closely related, though we do not understand the nature of the underlying mechanism.

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The hepatic circulation¹

STANLEY E. BRADLEY

Department of Medicine, Columbia University College of Physicians and Surgeons, and Presbyterian Hospital, New York City

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A VOLUMINOUS LITERATURE testifies convincingly, and sometimes eloquently, to the importance of the hepatic circulation in the body economy of vertebrates. The volume and composition of the blood perfusing the liver are undoubtedly major determinants of hepatocellular function. The maintenance of the hepatic parenchymal "milieu intérieur" with essential nutrients and the delivery of raw materials from the gut and other parts of the body to the liver for processing depends directly upon the blood supply. In even the lowest vertebrates the liver lies in the path of all the vessels draining the splanchnic viscera, thus potentially controlling the total splanchnic venous outflow (85). The splanchnic vasculature as a whole must be considered therefore an integral part of the hepatic circulatory system. The liver is influential in affecting general cellular metabolism and homeostasis only to the extent to which it can modify the chemical structure of the blood coming to it. A copious flow of blood is required for this purpose and the resultant anatomical arrangements and size of the hepatic vasculature appear to confer upon the liver an important place in cardiovascular dynamics.

Quantitative evaluation of the circulatory physiology of the liver and the other splanchnic viscera has proved extremely difficult owing to the inadequacies of the methods available, to uncertainties arising from species differences, and to the lack of data obtained simultaneously to provide information regarding the behavior of the remainder of the circulatory

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system. Measurements of cardiac output and arterial blood pressure are required to determine whether changes in hepatic hemodynamics are produced by local vasomotor activity or by passive changes in response to alterations in the perfusing pressure. Data on the correlated behavior of other vascular beds aid also in delineating the mechanism of integration and in placing the role of the splanchnic bed in proper perspective. Responses seem to differ between the various vertebrate species either because effective drug dosage levels and the intensities of the various stimuli used are not comparable or because the physiological mechanisms are fundamentally dissimilar. More data are needed to determine which of these alternatives is responsible for many phenomena. Meanwhile, interpretation of the behavior of the hepatic circulation in one species (in man for instance), on the basis of the known behavior in another (such as dog) must be made with caution. Methodology is a major stumbling block. Regardless of species, the hepatic circulation is difficult to approach and surgical procedures of some kind are usually necessary. As a result the method of measurement may modify or interfere with the response under study. Continuous observations over any extended period or repeated examinations at long intervals may be impossible owing to deterioration of the preparation or to the ultimate irreversible damaging effects of mensuration itself. All these difficulties may be laid to the inaccessibility and complex arrangement of the hepatic vasculature.

ANATOMY

Recent investigations have contributed importantly in characterizing the structural patterns of the hepatic vascular inflow and outflow systems. A variety of techniques has been employed. The injection of plastic masses and colored materials of various kinds into the hepatic artery, portal vein, and hepatic veins has been used with increasing skill and efficacy (97, 120, 148, 205, 214). Careful reconstructions by the wax plate method or by photographic procedures have resulted in a new appraisal of the arrangement of minute hepatic vessels relative to the parenchymal cells. Modern methods of microdissection have been less frequently used, but direct observation of the quartz-rod transilluminated liver in living animals has played an important part in providing information on the anatomy and behavior of the sinusoids (185, 270, 299). A large number of

careful gross dissections of the splanchnic vascular bed has resulted in more reliable statistical data on the various types of arrangements of the hepatic artery and portal vein (120, 145, 214). Although anatomical facts are of vital importance in the interpretation of functional data, it must be emphasized that a priori inference regarding functional significances on the basis of structure alone may be very hazardous.

The character of the venous and arterial inflow tracts is particularly susceptible to misinterpretation. The cross section of the hepatic artery is much smaller than that of the portal vein in a ratio of approximately one to five—suggesting that arterial inflow is roughly one-fifth of the portal venous inflow. Since this conclusion has found some justification in the measurement of blood flows, it has served to encourage further speculation. Cross-sectional area alone is not a good indication of relative flows in the absence of data on pressures and resistances, and it is not surprising, therefore, to find on further study that the only generalization regarding the relationship between arterial and venous inflow, which seems permissible at present, is that they tend to show a degree of reciprocity. Anatomically the two systems differ greatly.

The portal venous system drains the vascular beds of the spleen, pancreas, stomach, large and small intestines, and the mesenteries. Each of these beds presents certain unique features that cannot be dismissed simply because they are not immediately concerned with the hepatic circulation. The volume of blood flowing into the portal vein and the pressure maintained upon the blood in the portal vein are determined to a large extent by the resistances to arterial perfusion within each of these portal units. The dynamics of portal hepatic inflow are therefore bound up intimately with the behavior of extrahepatic splanchnic circulation.

The arteries giving rise to the extrahepatic splanchnic vasculature include a large array of major branches that spring directly from the aorta or from the celiac axis in a rather bewildering variety of patterns recently described in detail by several anatomists. [See (214) for survey.] In general there is an abundance of collateral anastomoses outside the organs supplied, but exceptions to this tendency abound and surgeons must proceed warily in ligating any large branch without prior demonstration of the area of supply.

The terminal vessels are equally diverse, ranging from the well-muscled end arterioles (penicilli) in

the spleen to the thin freely anastomosing mucosal arterioles in the gastrointestinal tract (22, 39, 184, 227, 317). It seems probable that the major point of splanchnic vascular resistance lies in these vessels, but arteriovenous (A-V) anastomoses between mucosal arteries and veins appear to be numerous. There is evidence (22) that blood may be diverted through these channels principally as a result of changes in capillary resistance rather than active changes in A-V cross section.

The capillary nets that drain into the various tributaries of the portal vein are also highly variable. In the gastric and mesenteric beds (22, 317) thoroughfare channels (A-V) may provide direct routing of blood from the arterioles to the venules, the degree of capillary filling outside the A-V capillary depending upon selective "sphincteric" action. Similar vessels have been described in the spleen. Here the capillary system is made more than usually complex by the presence of a venous sinusoidal system which has been the cause for much disagreement (184, 227). The presence of capillary sphincters and A-V channels elsewhere also remains disputed, since it is possible that the phenomena described may be artifactual. Muscular tissue is not obviously present in the capillaries or at the sites of the so-called "sphincters." Capillary vasomotion and the closure of sphincters may therefore be attributable to changes in intraluminal pressure secondary to arteriolar activity rather than local contractions. Capillary nets could contribute importantly to frictional resistance through mechanisms such as these, but further anatomical investigation is necessary. In addition, it must be shown more satisfactorily that the manipulation of tissues prior to or during microscopic examination is not responsible for the changes observed.

The portal vein enters the hilum of the liver in close relationship to the hepatic artery and the emerging common bile duct. It is a rather weakly muscled vessel, most of the muscle fibers being arranged longitudinally with a sparse coat of circular muscle (65). The structure of the portal vein suggests limited distensibility and easy collapsibility. Numerous communications between the portal vein and the systemic veins have been demonstrated by a variety of techniques. Edwards (119) has shown (by roentgenography and dissection after injection of a barium sulfate suspension into the femoral veins of three cadavers) that the most important connections are to be found in man at the retroperitoneal surfaces of the abdominal viscera, in the pelvis, and in the mediastinum. Even in normal persons,

the portal system fills with radiopaque material introduced in this way. The anastomoses are relatively small and are probably of no importance in determining portal venous pressure. They play a more prominent role when portal venous inflow is blocked. In dogs and other vertebrates in which mesenteries are better developed than in man such retroperitoneal links appear to be lacking (85).

At its entrance into the porta hepatis, the portal vein displays a relatively uniform and constant arrangement which contrasts sharply with the disorderly configuration of the hepatic arterial supply. According to Gilfillan (145) the portal vein is nearly always formed behind the head of the pancreas at the level of the second lumbar vertebra by the union of the splenic and superior mesenteric veins to course directly in the hepatoduodenal ligament to the hilum. The hepatic artery (or arteries), on the other hand, is highly variable in its origin, course, anastomoses within the gastrohepatic ligament, and relation to the portal vein. Within the liver, the venous and arterial inflow tracts assure a fairly regular pattern of distribution and relationships. At the hilum the blood vessels and bile ducts do not penetrate the capsule of the liver but are carried in a sheath of connective tissue derived from it which accompanies them in all their ramifications as the portal tract. Recent studies of vascular casts have demonstrated that the external fissuring or lobation of the liver is not precisely followed by the vascular and ductal system (173, 214). Instead the vessels are distributed to the right or left lobar segments which are separated by an avascular sagittal cleavage plane intersecting the visceral surface of the liver along a line drawn from the fossa of the inferior vena cava through the gallbladder. These "vascular lobes" are divided into segments which are distinct and easily separable in plastic corrosion casts. Communications between the right and left hepatic arteries or between their branches may be found within the liver (148) but appear to be uncommon, at least in man (84, 205). The portal venous system appears to have a similar and parallel arrangement with even fewer intrahepatic anastomoses.

The finer branches of the portal vein and hepatic artery communicate indirectly through a capillary network which appears to furnish the blood supply to the bile duct and other tissues in the portal tract (97, 120, 148, 185, 205, 214, 270, 299). The small hepatic artery lies close to the portal vein in all the vertebrate species studied. Arteriportal anastomoses resembling rungs of a ladder have been described by

some workers (185, 270, 299)—and denied by others (84)—in the frog, rat, mouse, rabbit, and guinea pig (not in the cat or man) close to the terminal arborizations in the portal tract. Three-dimensional reconstruction studies on the basis of injections of dyes or colloids by a large number of workers now seem to warrant the view that terminal branches of the hepatic arteries as well as of the portal vein give rise to the sinusoids in various mammals and amphibia (84, 97, 102, 120, 148, 185, 205, 214, 270, 299). It is possible that these findings apply in general to most vertebrates but additional studies of the comparative anatomy of the finer hepatic vessels are needed. The axial vein in the portal space appears to give rise to smaller radicles which then course parallel to the parent vessel, usually in the same direction, giving off branches that penetrate a so-called “limiting plate” of parenchymal cells to enter the sinusoids. Small branches leading directly into the sinusoid may also spring from the axial portal vein. The capillary network fed by the hepatic arterioles gives rise to the sinusoids and by its link to the portal vein provides an arterioportal anastomosis through which the portal venous distribution may be supplied by the arterial inflow; or the reverse could occur. It is difficult to be certain in the welter of conflicting claims, but it does seem likely that the sinusoids constitute the most important region of terminal arteriolar distribution rather than the portal tract and supporting tissues. The hepatic arterioles may join the terminal portal veins where they enter the sinusoids, or they may enter the sinusoids directly at any point between the portal tract and the central veins. The junction of the arterial and portal venous streams, therefore, apparently occurs chiefly (if not entirely) under most circumstances at or within the sinusoid and perhaps to some extent within the capillary network in the portal tracts. At this level the vessels appear to have very thin walls containing little if any muscle tissue. Sphincters are described at the point of entry into the sinusoid because closure of the vessels in a manner suggesting sphincteric action has been observed microscopically in transilluminated livers of living animals. Apparently muscular sphincters have not been detected by histological techniques. The point of emergence of a small capillary from a larger muscular arteriole in the portal space has been construed by Elias (120) as a sphincter. Certainly distinct muscular sphincters do not seem to be demonstrable within the sinusoidal system proper.

The structure of the hepatic lobule and the relationship between the parenchyma and the capillaries

or sinusoids has long been the subject of spirited discussion, and disagreement that is not yet settled. In recent years, Elias and his associates have taken issue with the view that the liver is a complex tubular gland modified by extensive coalescence and reorganization to form a tightly packed mesh of cells bathed on all sides by the blood in the sinusoids. They have called attention to the dominance of long rows of cells, one cell thick, in sections of mammalian livers and the paucity of cylindrical cross sections such as one might expect in a tubular organ. Careful three-dimensional reconstructions indicate that the liver may be considered a cell mass penetrated by a network of tubular sinusoids separated by interconnecting cellular sheets or plates, one cell thick in mammals and certain birds, usually two cells thick in all other vertebrates. A tubular layer of parenchymal cells encloses the portal tracts as a limiting plate which is pierced by the terminal branches of the portal vein and hepatic artery. The limiting plate can be traced along the tract to the surface of the liver where it passes out to lie under the capsule. There may be several such subcapsular (seemingly concentric) limiting plates or none. The openings into the central vein are so numerous that a clear-cut limiting plate is not demonstrable but a similar lamina does appear about the sublobular vein and layer branches of the hepatic veins. These studies have not definitely ruled out the possibility that the liver is basically a closely conglutinated tubular structure in lower forms, with flattening and realignment of the cells into single cell layers in the mammals. Indeed, a tubular construction is demonstrable when increased sinusoidal pressure increases the spaces between the laminae and seems to fragment them (121). Rappaport (237) and his associates have attributed the usual microscopic picture to the character of the basic hepatic unit which they believe to be an “irregular berry-like parenchymal mass situated around the trio of terminal branches of portal vein, hepatic artery, and bile duct, growing out from a small portal triad and mainly running perpendicularly to the central vein. The hepatic unit occupies adjacent parts of neighboring hexagonal fields and extends from the central vein of one hexagon to the central vein of another.” All sections of such a structure would tend to be tangential and would, they claim, yield a preponderance of longitudinal sections.

Regardless of the ultimate outcome of this argument it is evident that sinusoids are cylindrical or saccular vessels closely encased in a kind of highly flexible plastic sheathing that must operate to in-

fluence their behavior. They radiate from the portal tracts and converge upon the central veins, producing the appearance in section of hexagonal "lobules" that are centered upon the central vein. This appearance is apparently attributable to the degree of filling of the peripheral vessels between the portal tracts, since it has been shown that elevation of hepatic venous pressure or reduction in portal venous pressure changes the configuration of the lobule to one centered upon the portal tracts as a result of relative distension of the vessels running between the central veins (121). The walls of the sinusoids are composed of thin endothelial cells, possibly [as Knisely *et al.* (185) claim] all capable of active phagocytosis, though this question is not yet settled. There is no evidence of muscular tissue and the endothelium is usually closely attached to the parenchymal cells. A narrow perisinusoidal fluid-filled (plasma?) space (Disse) observed on many occasions by light microscopy has been clearly delineated by the electron microscope (30, 126, 169). Numerous relatively large fenestrations in the sinusoidal endothelium may permit the plasma to come into direct contact with the hepatic cells. Both luminal and the canalicular surfaces of the parenchymal cells are markedly increased by folds and microvilli. The space between the endothelium and the polygonal cells is apparently no greater than 0.5μ and it may be filled with an amorphous material resembling basement membrane rather than plasma. Since the extravascular space is so narrow, the sinusoidal closure must involve displacement and apposition of the surrounding cell plates.

The hepatic venous drainage system begins in the colander-like thin-walled central veins that empty into the muscular sublobular veins. In certain respects the central veins appear to be passive sumps not strictly separable from the parenchyma and not unlike a large receiving sinusoid. Opening and closure of sinusoids at the point of entry into the central vein have been described by workers using transillumination techniques (186), but definite structural evidence of muscular sphincters seems to be lacking. In contrast the muscle coats of the "sublobular" and other hepatic veins appear to be entirely adequate for this purpose. Gibson (143) finds that sinusoids empty only into the central veins although Deysach (107) has claimed that sinusoids may occasionally enter the larger hepatic venules directly as "sluice channels" which may bypass the central venous sumps. Gibson believes these vessels are really central veins and he agrees with Deysach

in viewing the point of passage through the thick muscular wall as a site at which contraction could interfere with flow. In the dog, contraction of the musculature can throw the large as well as the small hepatic veins into corrugated folds that could conceivably block outflow completely (287). The extent of this musculature appears to vary greatly in different species, but it appears to be weak and relatively unimportant in man (132, 143). The distribution of the hepatic veins and their tributaries results in an intimate interdigitation with the system of portal tracts. The finer radicles course at acute angles or perpendicular to the portal tracts from which they are derived. There is no evidence of segmentation or lobation as there is in the arrangement of the portal tracts. Except in animals with deeply fissured and lobated livers, the hepatic veins freely cross the "avascular plane" separating the hepatic segments to bind the liver into a single vascular mass. The system empties into the inferior vena cava by three or more terminal branches just below the diaphragm or within the "caval tunnel" where the inferior vena cava is closely applied to or incorporated in the posterior surface of the liver. In certain species (notably the dog and diving mammals) the muscular coat of the hepatic vein becomes more prominent and forms a sphincteric ring at the orifice into the vena cava. The preponderance of the inferior portion of the ring may serve as a "sling" to pull up the lower lip of the opening into a valvelike ridge.

A lymphatic drainage system runs parallel to the vascular inflow and outflow tracts, to communicate at the hilum and at the junction of the hepatic veins and inferior vena cava with larger trunks that ultimately carry the lymph through the local lymph nodes to the cisterna chyli or thoracic duct (85). A rich network of lymph vessels lies about and within the walls of the draining vessels and beneath the capsule of the liver, but there is little evidence for lymphatic capillaries within the parenchyma. It is possible that the perisinusoidal space is the terminus a quo of the lymphatics. A more definite point lies in fluid-filled spaces, the so-called spaces of Mall, found in close proximity to the portal tracts, between the limiting plate and the connective tissue making up the bulk of the tract. Arrangements of cells and channels resembling very small lymph nodes are described or pictured at many points within these nets and a rich lymphopoietic layer is found beneath the capsule of the liver in some of the lower vertebrates. Erythropoietic tissue may also occur in adult

forms, though it is usually more prominent in fetal livers (120).

The liver is a remarkably malleable organ, the adjoining organs molding its surface and determining its shape. Changes in the filling of the stomach in the dog, for example, induce considerable alteration in the configuration of the portion of the liver lying in contact with it. The influence of these deformations on the local hepatic circulation does not seem to have been studied. It is likely that only the more superficial parts of the liver are involved and that resistance to flow is increased in the compressed regions. The liver appears to be equally plastic when interference with outflow, as in congestive heart failure, results in an elevation in vascular distending pressures. Presumably the marked hepatic enlargement involves stretching of lamellae, canaliculi, and the connective tissue framework (121). To what extent the distortion affects the degree and distribution of resistance to blood flow remains undetermined. Certainly, if the distortion is long maintained, persistent change in architecture occurs and fibrosis develops.

METHODOLOGY

The structure and location of the hepatic vascular bed and its tributaries indicate at once the physical difficulties of quantitative evaluation of hepatic hemodynamics and the variety of measurements required. Among the latter the following appear to be particularly important: *a*) determination of the minute volumes of blood flowing into and out of the liver, including flows through the various components of the splanchnic bed; *b*) measurement of the volume of blood within the hepatic vascular bed and the contributory vessels of the splanchnic viscera; and *c*) measurement of the blood pressure in the arteries, the hepatic veins, and at the points of junction between the different streams in the portal vein and the sinusoids. Given these data, a complete analysis of the local determinants of flow and integration is possible. Until recently, most hepatic hemodynamic parameters have been measurable only by a direct approach involving considerable traumatic manipulation and interference with normal function. Various indirect methods are now under study in many laboratories which appear to provide a means of measuring local blood pressure and hepatportal blood flows and volumes in intact animals and man without operation or anesthesia.

Direct Methods

HEPATIC AND SPLANCHNIC BLOOD FLOWS. Blood flow through the hepatic artery, the portal vein, and hepatic veins has been measured directly in experimental animals for many years by a number of devices. The Ludwig stromuhr has been replaced by the thermostromuhr and more recently by the rotameter and other types of flowmeter (67). These methods require isolation of the artery or vein for insertion or application of the measuring device. Additional surgery is required to obtain a value for hepatic venous outflow by difference between the flows through the inferior vena cava above and below the entry of the hepatic veins or as the retrograde flow through the inferior vena cava (above the renal veins) after ligation at the level of the diaphragm. Trauma, anesthesia, manipulation, hemorrhage, and loss through collateral channels all contribute to the errors inherent in these procedures. Nevertheless, they possess the great advantage of the direct approach.

The so-called "collection methods" are equally direct but somewhat easier to use and more accurate, at least with respect to the measurement of hepatic venous outflow and portal venous inflow. Here the outflow is collected, rapidly measured, and then returned to the systemic circulation. Thus, portal venous inflow may be measured as the outflow from the severed splenic vein following splenectomy and temporary occlusion of the portal vein close to the liver (204). Blalock & Mason (35) introduced under local anesthesia a blind brass cannula with lateral openings via the right external jugular vein of the dog, the superior vena cava, and right atrium into the inferior vena cava where balloons affixed to the cannula could be inflated temporarily at points above and below the entry of the hepatic veins during withdrawal of the total venous outflow. More recently, Selkurt (264) has measured hepatic venous outflow in dogs by a similar technique after shunting blood from the hind portions of the animal via an external circuit from the femoral veins to an external jugular vein, with ligation of the inferior vena cava below the hepatic veins, and collection of hepatic venous blood from above by a special cannula. Although this method requires general anesthesia and abdominal surgery, inclusion of blood from the lower portion of the vena cava is avoided and a period of complete obstruction of flow from the hind portions, with attendant circulatory disturbances, is circumvented.

Changes in local blood flow and velocity may be detected by instruments recently developed upon the principle of the "thermostromuhr." Grayson (155) and his associates have used a tiny copper-constantan thermocouple and heating wire implanted in the liver for this purpose. The measured loss of heat to the tissues appears to be a linear function of tissue thermal conductivity and blood flow. The first of these variables may be determined as a constant for each liver after cessation of circulation; changes in the second can then be computed in percentage terms from changes in conductivity. The unit may be left in place indefinitely and measurements made as desired after healing of the wound through which the leads emerge. Movement of blood can be assessed only in a collar of tissue approximately 0.5 cm long and 0.3 cm in diameter within the immediate vicinity of the embedded thermocouple. Although total flow cannot be measured, the instruments provide a satisfactory means of following either acute or chronic adjustments in small animals. A somewhat similar device has been introduced by Grabner & Neumayr (151) for the purpose of estimating blood flow through a hepatic vein. A tiny thermistor affixed to the tip of a Cournand catheter is heated several degrees above the temperature of the blood after insertion into an hepatic vein. Any change in temperature of the element is directly related to a change in the velocity of the blood flow in the immediate vicinity of the "pickup," or to the actual volume of flow if the calibre of the vein is constant. Movements of the catheter tip with respiration, reversal in the direction of flow, scar formation, proximity of large vessels, and changes in hepatic blood temperatures may jeopardize the validity and usefulness of the method, but it does possess the advantage of detecting rapid and transient alterations.

The transillumination method (185, 270, 299), discussed above in connection with the delineation of the finer anatomy of the liver, has proved valuable in defining the character of blood flow through the terminal radicles of the hepatic artery and portal vein. The technique involves careful exposure of the liver in anesthetized or pithed animals with as little trauma and blood loss as possible. A quartz rod, provided with a conduit through which warm Ringer's solution may bathe the tissue examined, must be inserted under the edge of the liver. The liver edge transilluminated by light conducted through the quartz rod may then be examined microscopically at high magnification. Respiratory movements of the liver can be prevented in the anesthetized ani-

mals by the introduction of 100 per cent oxygen through a catheter placed in the trachea. Fluorescence microscopy and transillumination with ultraviolet light following injection of fluorescent materials permit somewhat better visualization of the blood stream within the sinusoids and of the movement of the materials from the blood into the parenchymal cells and bile canaliculi (153). Dyes and particulate substances have been used similarly to follow flow in visible light. The conditions under which observations must be made are obviously unphysiologic and limit the extent to which generalizations may be adduced. Local extraneous factors such as changes in tissue tension, the direct effects of immobilizing and handling the liver, the influence of foreign materials and fluids within the abdominal cavity, as well as the effects of anesthesia, prolonged immobilization of the body in an abnormal position, and the limited area available to study combine to make interpretations most uncertain. When considered in relation to information obtained by other methods, however, studies of the transilluminated liver may be most helpful and revealing.

Studies of the perfusability of the isolated liver have also contributed to the knowledge of the hepatic circulation, though here again interpretation in terms of the intact animal and the circulatory system as a whole must be made with caution. The preparation of the liver in investigations of this kind has varied widely. At one extreme the liver is handled with greatest care to avoid prolonged interruption of blood flow either by perfusing the liver in situ or by rapid transfer from the living animal to the perfusion apparatus where it is maintained under conditions as closely as possible approximating those in situ (10, 25, 61, 83, 277). The contributions of the arterial and venous inflow to total outflow, the character of intrahepatic adjustments, and the response to an array of controlled pressure-flow states impossible to impose in the intact animal may be precisely evaluated in the isolated perfused liver. Techniques have steadily improved with the development of more effective anticoagulation, oxygenation, and surgery. At the other extreme, the liver is removed at a varying time after death and perfused with different foreign substances, ranging from saline to kerosene (111). Intrahepatic resistances and the interplay of the inflow systems at different pressures have been evaluated by this means. Kerosene oil has been used by Dock (111) because it is confined to the vascular channels and does not diffuse, as saline solutions do, into extravascular tissues

to interfere with perfusability. As noted above, the injection of colored plastic semisolid substances aids in defining functional relationships between vascular structures as well as their anatomic arrangements. The extent to which streams of different color intermingle or fill a given portion of the vascular bed points to dynamic relations that may be important in life.

Radiopaque injection masses have been used in both living and "dead" livers in order to visualize the vascular tree by X ray (22, 84, 148). Daniel & Prichard (102) have used microangiography to study portal venous flow in rats, cats, guinea pigs, rabbits, and goats. Contrast substance is injected rapidly into an omental or intestinal vein and serial radiographs taken thereafter at a rate of one or two per sec over a 9- to 12-sec period or motion pictures by high-speed cinefluorography (144). The dispersion of the radiopaque material in the blood stream, the distribution of portal inflow to the hepatic segments, and the time of blood movement may be determined graphically in this manner. Although there are obvious drawbacks (anesthesia, immobilization, the presence of a foreign material in very high concentration, and manipulation of the gut), certain hemodynamic effects can be examined only by this method.

Radiographic methods of studying the portal venous system have also proved of value diagnostically. Roentgenograms taken at the operating table immediately after injection of a concentrated solution of Diodrast (85) (70%—12 to 40 ml, depending on the size of the patient) or Urokon (70%—in similar dosage) into a tributary of the portal vein have been helpful in determining the extent of collateral circulation or the point of venous obstruction in patients with portal venous hypertension. Percutaneous splenoportal venography (15, 314) permits visualization of the splenic and portal veins in anesthetized patients and, when rapid serial radiography is employed, the character of blood flow and vascular filling can be made out. Diodrast or Urokon may be injected directly into the spleen through a long 17- or 18-gauge needle that is inserted through the skin under local anesthesia. In most patients, subjected to this procedure, the spleen is palpable and the needle may be placed obliquely into the body of the spleen, or it may be introduced through the ninth intercostal space at the midaxillary or posterior axillary line. The contrast substance leaves the spleen almost at once and may be detected radiographically within one or two seconds in the portal vein and its branches. The procedure is somewhat hazardous,

since intraperitoneal bleeding often occurs and splenic infarcts may develop. Severe hemorrhage has been reported.

Of even greater potential danger is a new variant of the technique of splenoportal venography described by Bierman and his associates (32), who introduce a needle through the liver into the portal vein. However, they report that no serious complications developed following or in the course of 144 transhepatic portal venipunctures in 73 seriously ill patients. Under local anesthesia, while the patient holds his breath, they insert a special large-gauge styletted needle at a point 1 cm below the xiphoid process and 1 cm to the right of the midline to a depth of 12 cm. The obturator is then removed and the needle is slowly withdrawn during application of gentle suction until there is free flow of blood, indicating that the laterally placed orifice lies in a vessel. A small ureteral catheter or polyethylene tubing may be threaded through the needle into the vein and left in place for a prolonged period after the needle has been withdrawn. A contrast medium such as Diodrast, Urokon, or Neo-Iopax (sodium acetrizate, iodopyracet, or sodium iodomethamate) may be injected through the needle or catheter. In a number of instances, the hepatic vein, inferior vena cava, or hepatic artery have been visualized. Zeid *et al.* (314) have had a similar experience. A more recent development which employs the costal intra-osseous route appears to be considerably safer (262). The injection of contrast material directly into the medullary cavity of a lower rib results in visualization of veins in the vertebral, intercostal, azygos, and hemiazygos drainage system. In contradistinction to splenoportal venography, which reveals portal collateral channels in the presence of portal hypertension, intraosseous venography permits detection of systemic venous collaterals.

HEPATIC AND SPLANCHNIC BLOOD VOLUMES. The volume of blood in the liver and the splanchnic bed may also be estimated by radiographic and injection techniques. The relative mass of the hepatic vasculature has been evaluated qualitatively from venograms and arteriograms, and from the volume of plastic casts of vascular tree. Measurement of the liver opacified by contrast medium or delineated after inflation of the stomach or colon with gas is also theoretically possible (300). Changes in the size of the spleen have been followed radiographically (20) and interpreted in terms of displacement or filling with blood. Unfortunately, the extent of vascu-

lar filling by contrast substance or injection mass is most uncertain, and the assumptions required in estimating volume from X-ray shadows are of dubious validity. Nevertheless, further exploration in this direction may prove fruitful.

Changes in the volume of spleen and liver may be more accurately measured plethysmographically in animals, but the fixation of the organ and the surgical handling required seriously impair the validity of the values obtained (132). These devices permit a rough estimation of engorgement or disgorgement of the liver during vascular adjustments, but they provide no information on the absolute volume of blood in the liver. The same difficulties are encountered in studies of the volume or weight of the isolated liver (10, 25, 61, 203) or spleen (163, 287). Measurement of the volume of blood retained in or expelled from the liver or splanchnic bed as a whole may also be made on the basis of the difference in blood inflow and outflow during a period of shifting volume.

It has proved extremely difficult, also, to determine the absolute volume of blood in the liver or spleen and their tributaries by the direct approach. With excision, blood runs off into the systemic veins and is lost. Surgery in living animals, with care to block inflow and outflow tracts simultaneously and to avoid trauma that might induce physiologic redistribution of blood, is required to obtain reliable values. The quantity of blood may then be evaluated by extraction of hemoglobin and calculation of blood volume from the hematocrit of arterial blood. A serious difficulty arises at this point because the hematocrit in the capillaries and sinusoids may differ greatly from that in large vessels. Radioisotope labeling of plasma (I^{131} -labeled human serum albumin, Cr^{51} tagging of plasma proteins, T-1824 bound to plasma proteins) and of red cells (P^{32} , Cr^{51}) has proved helpful in surmounting this obstacle. Recovery of the isotope is relatively easy and blood volume can be calculated on the basis of the radioactivity per unit volume of arterial plasma and red cells. Allowance must be made for the possible uptake of radioisotope by the liver cells or lymph. Though these methods (106, 175, 181) provide approximate values for hepatic blood volume in steady states, changes in the same animals cannot be obtained.

HEPATIC AND SPLANCHNIC BLOOD PRESSURES. Blood pressure has been measured directly in the intra-abdominal veins after laparotomy in animals and man (85). Opening the abdomen may bring about changes in

pressure gradients independently of the effects of anesthesia and surgery, but on the whole these measurements are acceptable and revealing, particularly when analyzed in terms of simultaneous measurements of arterial pressure and blood flow. Pressure measurements may be made in unanesthetized subjects by percutaneous splenic or hepatic puncture (15, 17, 32). Atkinson & Sherlock (17) found a statistically linear correlation between intrasplenic pressure and portal venous pressure over a wide range in 24 patients. With transhepatic puncture of the portal vein (32) reliable records may be obtained that possess an advantage over intrasplenic pressure tracings in showing phasic or respiratory fluctuations that are damped out in the splenic pulp spaces. Portal venous pressure has also been estimated on the basis of pressure in large readily accessible collateral veins in the abdominal wall of patients with portal venous obstruction. Though this approach may yield valid figures for the subject under study, it is not feasible in the normal and does not yield values of general application. Care must be taken to refer all values to the same reference plane, preferably at the level of the right atrium determined radiologically. Many workers use a level 5 cm posterior to the angle of Louis as the reference plane in human subjects; and in general this is quite satisfactory, though it appears to be a less dependable guide to the level of the right atrium than the plane 10 cm anterior to the back (246). Changes in pressure are usually of particular interest and the importance of the zero reference plane is not often stressed, since the accuracy of pressure differences is not affected by it. When absolute values obtained by different groups of workers are compared, however, apparent discrepancies are encountered that may be due to inexact definition of the reference point.

The development of venous catheterization techniques by Cournand, Richards, and their associates (98, 246) has opened up a new approach to the study of intravascular pressures. The insertion of a long radiopaque ureteral catheter deep into the venous system under fluoroscopic control is atraumatic, relatively simple, and safe. The catheter is introduced under local anesthesia into a vein in the antecubital fossa (preferably lying at the medial aspect) in human subjects and into a jugular vein in dogs. It is then threaded into the right atrium and inferior vena cava. A curved tip makes manipulation and control of direction possible but at the same time interferes with passage, since it may cause the catheter to move in unintended directions or to catch at valvelike

shelves, such as the Eustachian "valve" in the right atrium at the point of entry of the inferior vena cava. With experience it is usually possible to maneuver the catheter tip past these obstacles and into the desired vessel. Human subjects can assist in this operation by making voluntary movements of the arms, shoulders, neck, and trunk or by deep breath holding, thus shortening, lengthening, or straightening the venous channels in accommodating the passage of the catheters. Untrained dogs must be anesthetized and external movement of the body employed as an aid. Rappaport (77) has described a device for "guided catheterization" which can be used to bend the tip of the catheter after it is placed close to the orifices of the hepatic veins. The angulation obtainable permits catheterization of an hepatic vein from below, an approach which is impossible with the Cournand catheter owing to the relatively fixed obtuse angle of its tip. In at least 1000 catheterizations of the hepatic veins in man in several laboratories not a single fatality has occurred despite the fact that many subjects were seriously ill. This good record is undoubtedly attributable to the fact that the right heart is not entered and thus a dangerous source of arrhythmia is avoided. The use of a relatively soft catheter is advisable even though it makes manipulation more difficult. Excessive buckling or coiling should be guarded against, since knots can be tied in the catheter. Indeed, a knot in a catheter which included the chorda tendinae of the tricuspid valve has been observed in the dog. The procedure is therefore not without hazard and should always be used cautiously with the catheter under direct observation throughout. In man, a vein draining the right lobe is easiest to enter; in the dog, a vein draining the left lobe. Since these lobes are the largest hepatic lobes in man and dog, the catheter can be inserted to a depth that permits reliable measurements of intrahepatic venous pressure.

Taylor & Myers (286) have shown that thrusting the catheter deep into the liver and obstructing the hepatic vein provides a means of measuring portal venous pressure. Occlusion is assured by introducing the catheter until it buckles slightly within the hepatic vein. The "occluded hepatic venous pressure" theoretically reflects the pressure transmitted from the portal vein or venules through a stationary column of blood extending from the tip of the catheter. The outflow tract obstructed is probably quite large, presumably consisting of a "wedge" of convergent hepatic venules, sublobular veins, and sinusoids into which both hepatic arterioles and portal venules

empty. The hepatic venous "end pressures" therefore may mirror the mean pressure attained when flows into and out of the obstructed area have reached equilibrium and may more closely approximate sinusoidal pressures than portal venous pressure. The small gradient of pressure between the portal vein and the sinusoids probably accounts for the good agreement with the portal venous and intrasplenic pressures reported by a number of workers (76, 135, 244).

Indirect Methods

Hepatic venous catheterization has also proved of major importance in the development of indirect methods for the appraisal of the hepatic circulation. Accurate measurement of changes in the blood as it passes through the liver makes it possible to apply the Fick principle in the estimation of flow, to study hepatic clearances, and to follow the dilution of isotopes within the splanchnic blood volume. Since hepatic blood flow and hepatic arteriovenous differences can be determined simultaneously, hepatic removal of various substances from the blood can be subjected to analysis. Under appropriate conditions maximal hepatocellular activity can be employed as a means of approximating the mass of tissue perfused by blood in order to permit more precise definition of ischemia, hyperemia, and redistribution. On the basis of such analyses, more sophisticated clearance techniques have been developed that may circumvent venous catheterization. The blood volume in the splanchnic bed and the distribution of flow and volume have been adduced from studies of the time required for the movement of tracers such as I^{131} human serum albumin across the splanchnic bed, in relation to flow. These approaches have been opened up in the past 15 years and are already yielding a rich harvest of new information regarding hepatic hemodynamics.

HEPATIC BLOOD FLOW. The hepatic blood flow can be estimated indirectly by three somewhat different methods. In one the total quantity of some substance removed from or added to the blood each minute by the liver is determined and divided by the hepatic arteriovenous concentration difference, i.e., the amount removed from or added to each milliliter of blood perfusing the liver. In a second procedure, the percentile disappearance of some substance more or less completely cleared from the blood perfusing the liver is measured and hepatic blood flow

computed as that percentage of the blood volume. And, finally, flow may be estimated from the extent of dilution of a known quantity of some tracer by total outflow during a measured period of time. Obviously, the validity of all measurements depends upon a number of assumptions which are difficult to verify. Nevertheless, suitable test substances have been found and adequate evidence of reliability has been forthcoming to warrant qualified acceptance of much of the data set out in the literature.

Clearance and extraction techniques. A variety of dye-stuffs has been employed in the development of constant infusion clearance and extraction techniques beginning with bromosulphthalein (BSP or Brom-sulfalein) in 1945 (49), and more recently employing tetrachlor-tetraiodo-fluorescein (rose bengal) (258), and a tricarboyanine dye, indocyanine green (238, 304). The hepatic removal of these substances can be estimated with reasonable accuracy from the rate of infusion if it may be assumed that *a*) disappearance from the blood depends solely upon hepatic extraction, and *b*) changes in plasma concentration can be taken into account simply by multiplying the change in concentration (ΔP) by the plasma volume (PV). Subtracting (rising level) or adding (falling level) this product (in milligrams per minute) and the infusion rate yields a value for hepatic removal. The hepatic arteriovenous difference is measured as the difference between concentrations in samples of blood obtained from a peripheral artery and an hepatic vein at the same time. As a rule these values are derived by interpolation at the midpoint between successive samples in order to allow for simultaneous correction for changing levels. A number of additional assumptions must be made in accepting this procedure including *c*) that a sample of blood from any hepatic vein is representative of the total mixed hepatic venous drainage; and *d*) that the presence of the catheter does not affect representative sampling. Numerous thoroughgoing investigations have elucidated each step and in doing so have contributed importantly to knowledge of hepatocellular function.

All these agents are apparently transferred from blood to bile by fundamentally similar mechanisms. The character of BSP removal has been the most intensively studied but the data available on rose bengal and indocyanine green suggest that they move by the same pathways, since indocyanine green interferes with hepatic uptake of BSP (304) and BSP with uptake of rose bengal (177, 212). Considerable evidence (45, 59, 75, 177, 212, 305, 306, 312) supports

the view that BSP is removed from the blood by a dual mechanism that involves *a*) accumulation or "storage" of the dye within the polygonal cells in a higher concentration than in the plasma, and *b*) transfer by a limited transport system from plasma to bile. Analysis of the biochemical mechanisms of further subsidiary processes and of the physiological concomitants is far from completion, but it seems not unlikely that both storage and transfer require energy expenditure and depend upon enzymatic catalysis. Uptake into storage apparently proceeds only when the plasma concentration is rising and for a period after stabilization until equilibration is complete. Whether BSP moves into the bile only from the so-called "storage space," directly from the blood to the bile canaliculi, or by both routes remains unsettled. Rose bengal appears to be handled in much the same fashion and may indeed be visualized by fluorescent microscopy as it accumulates in high concentration within the parenchymal cells. Intercellular accumulation of indocyanine green has not been proved but seems probable in view of the rapidity with which it disappears from the blood relative to its output in the bile (304). The limit imposed upon removal by the transfer maximum or T_m^2 results in reduced extraction by the liver as arterial plasma concentrations rise and makes it preferable to maintain levels close to 1 or 2 mg per cent in order to assure sufficiently large differences between peripheral and hepatic venous concentration for accurate measurements. Even at higher levels, however, hepatic removal accounts almost exclusively for the disappearance of these substances from the blood.

Considerable confusion has resulted from failure to use such words as "removal," "extraction," and "recovery" with precision. "Removal" may be defined either as the amount of dye removed from the blood each minute (the usage employed in this

² Unfortunately the term L_m has been applied by Mason *et al.* (208) to maximal hepatic removal of BSP. Maximal transfer is determined by liver mass and the abbreviation, L_m , is, therefore, justified to some extent. Nevertheless, transfer is a functional phenomenon that may be affected without change in liver mass by substances competing for the same system, by various inhibitors (such as deoxycholic acid or Benemid in the case of BSP), and by fever or hepatic disorders (74, 306). For this reason use of " T_m " to refer to the "transfer maximum" seems preferable and in keeping with usage in other fields (280). Of even greater importance is the fact that L_m as determined by Mason (208) and others (285, 295) includes movements of dye into storage as well as transfer from blood to bile. Hence in referring to a more discrete (albeit complex and multifarious) activity T_m appears to be the more suitable term.

paper) or as the total amount which has appeared in the bile over a period of time—usually several hours and usually expressed as a percentage of the total dose administered. The latter is also often referred to as “recovery” but may be confused with “extraction,” a term correctly applied to the percentage of dye removed from the blood perfusing liver and calculated as the ratio between the arterial-hepatic venous concentration difference and the peripheral arterial or venous concentration. Hepatic extraction must be computed on the assumption that the arterial concentration is a measure of the concentration in the blood perfusing the liver by way of both the hepatic artery and portal vein from which extraction has occurred to account for the concentration found in the hepatic venous blood. For this reason due allowance must be made for splanchnic circulation time when rapid changes are occurring.

Perhaps the most serious confusion has arisen in discussions of extrahepatic removal of BSP. When the plasma level was maintained at a constant level in the dog at about 1 mg per cent, the extraction of BSP averaged $34 \pm (\text{SD}) 12$ per cent (282), in association with removal rates of from 0.57 to 1.98 mg per min. No more and usually much less than 10 per cent of the amount removed per minute could be ascribed to extrahepatic loss, when direct measurements of hepatic uptake of BSP were made in the anesthetized dog (41, 305). Following hepatectomy, however, the plasma level may fall by 25 or 35 per cent from a level of 1 mg per cent 1 hour after a single intravenous dose, an observation which has been claimed (87, 88, 302) to indicate a proportionately large extrahepatic contribution to removal. The confusion here stems from comparing two fundamentally different removals; one, the percentage of the total removal rate per minute attributable to extrahepatic tissues; the other, the percentage change in plasma concentration over the course of 1 hour. If the dog's circulating plasma volume following hepatectomy can be taken as 800 ml, then a 30 per cent fall in BSP from a concentration of 1.0 mg per cent to 0.7 mg per cent in the course of 1 hour would entail a total loss of 2.4 mg or 0.04 mg of BSP per min, approximately 5 per cent of the expected removal of 1.0 mg per min. This figure does not differ greatly from those obtained by direct measurement and it may be concluded that extrahepatic loss is negligible under most circumstances. The failure to escape from the vasculature may be attributed to the fact that all three dyes are almost completely bound by the plasma proteins (49, 258, 304). Neither rose bengal nor

indocyanine green enters the urine (258, 304), whereas Bromsulfalein is excreted by the kidney in amounts equaling 0.06 to 2.0 per cent of the total dose (49, 60, 88, 220, 232, 275, 311). Since disappearance from the blood depends, therefore, almost exclusively upon the liver, hepatic removal per minute may be computed from the rate of infusion (plus or minus, respectively, the amount removed from or added to the plasma volume, i.e., $\Delta P \times PV$). This conclusion is not vitiated by failure to “recover” more than 60 to 80 per cent of a dose of BSP from the bile nor is indocyanine green necessarily preferable because 97.7 per cent of a single dose appears in the bile. The total recovery is a measure of the extent to which other excretory pathways are accessible and of the time allowed for collection. It does not throw light upon the movement into other tissues.

The incomplete recovery of BSP does suggest, however, that BSP may undergo alteration in the body and that, as a consequence, calculation of hepatic removal may be erroneous. Brauer and his associates (60, 188) have shown that BSP from the bile of the cat, rat, sheep, and chicken can be separated into four fractions by column chromatography having the same absorption spectra. Recent work (45, 93, 105, 165, 178, 211) indicates that the chromatographic fractions are conjugates of BSP formed in the liver by combination with glutathione at the sulfhydryl group (GSH), with the release of bromine. Since GSH is confined to the cells, conjugation must occur intracellularly. In addition to various isomers of BSP-GSH, BSP-cysteinyl-glycine conjugates are formed, presumably by enzymatic hydrolysis of BSP-GSH, since free glutamic acid appears simultaneously in the bile. There is at present no evidence that conjugation is essential to transfer or storage of BSP (178). Indeed, free BSP appears in the bile and both rose bengal (189) and indocyanine (304) are excreted without any evidence of conjugation. All the biliary BSP conjugates have been found in the blood of man and dog indicating escape from cells. This movement into the blood occurs chiefly within the liver and does not interfere with the calculation of estimated hepatic blood flow (EHBF) since it affects the computation of both hepatic extraction and removal to the same extent and thus cancels out. Enterohepatic circulation (198, 199, 224) of dye is similarly of no concern provided hepatic venous concentration does not exceed the arterial concentration and provided portal venous blood does not bypass the liver via collateral pathways. In any case, in-

testinal absorption of BSP, though it does occur, does not seem to result in a significant difference between portal venous and arterial concentrations. Whether derived from intestinal contents or from hepatic cells, BSP conjugate displays the same spectral properties as standard BSP, but its extinction coefficient appears to be slightly different (188). The error so produced also tends to cancel out. A larger error may result from conjugation that occurs elsewhere in the body, as in the kidney (252). However, BSP conjugate from this source seems to contribute insignificantly to the blood level, even in hepatectomized dogs with prolonged maintenance of very high plasma BSP concentrations. BSP conjugate accounted at most for 10 per cent (1.0 mg per cent) of the plasma BSP concentration 45 min after administration, with plasma levels falling from 17 to 10 mg per cent, in two dogs studied by Rosenau and his associates (252).

The most important drawback in the use of BSP, rose bengal, and indocyanine green for the measurement of hepatic blood flow lies in the impossibility of sampling a mixture of all the venous blood draining from the liver. The liver is a large organ in which nonuniform perfusion, inequalities in tissue activity, and heterogeneity of bile formation may be induced at any time by a large number of extraneous factors. Nevertheless, many workers (77, 146, 232, 275) have failed to find any significant difference between concentrations of BSP in blood taken from different hepatic veins in the same animal, provided peripheral plasma levels are kept constant and comparable. Differences observed by others (49, 118) may be ascribed to changing concentrations or to sampling difficulties. Careful control is especially important during withdrawal of blood through the catheter in an hepatic vein (62, 118, 146, 257). Diaphragmatic movements result in displacement of the tip of the catheter by pressing the liver down and in doing so predispose to retrograde suction of blood from the inferior vena cava. In the dog, contraction of the hepatic venous musculature seems occasionally to block venous outflow from the liver without interference with reflux. Since this phenomenon occurs infrequently and erratically, it is extremely difficult to appraise quantitatively. Edwards' (118) failure to observe it in three experiments is therefore not surprising. As he notes, hasty sampling may result in dilution by residual "washout" saline infusion trapped in the catheter and veins. Care must be taken to avoid wedging the catheter deep in the

hepatic vein in order to avoid any stimulus to hepatic venous contraction or interference with outflow.

Of special importance is the fact that obstruction by the wedged catheter may affect portal venous inflow preponderantly so that the sample obtained consists largely of blood originating in the hepatic artery. Sapirstein & Reininger (257) have reported values for sodium *p*-aminohippurate (PAH) concentration in "wedged" hepatic venous samples during mesenteric venous infusion of PAH that suggest such a possibility. Although their results may be explained by nonuniform distribution of PAH attributable to "streamlining," a recent paper by Brauer *et al.* (62) brings forward new evidence supporting the idea of interference with portal venous inflow by the catheter. These workers have injected S³⁵-labeled BSP into the portal vein or hepatic artery as a means of differentiating arterial and venous components in the outflow. With the former, radioactivity remained much lower in the hepatic vein than in the femoral artery, whereas radioactivity rose promptly in the hepatic vein and remained higher than in the femoral artery when BS³⁵P was injected into the hepatic artery. This phenomenon would not affect determination of BSP extraction if BSP were removed to the same extent from hepatic arterial and portal venous inflows. Andrews and his associates (14) have claimed that extraction is in fact more complete when BSP is infused into the hepatic artery than when it is given by the portal vein in perfused canine livers. Other workers (62, 83) have failed to confirm this observation, however, and in a variety of critical studies have found little difference in efficiency of extraction between the two routes. Nevertheless, the uncertainties inherent in hepatic venous sampling call for caution in interpretation and should be acknowledged by referring to the measure as "estimated hepatic blood flow" or EHBF.

The best evidence that clearance and extraction techniques with constant infusion yield valid estimates of hepatic blood flow has been obtained from simultaneous measurements by direct methods. Selkurt (264) found that the BSP method overestimated flow by 7.3 per cent on the average when total hepatic venous outflow was measured by collection and reinfused in 274 comparisons in 14 experiments. Similar results have been obtained by Shoemaker (275) and by Drapanas and his associates (114) using other direct methods. Changes in blood flow following hemorrhage or transfusion were accurately reflected in values for EHBF. In view of unavoidable trauma and blood loss that would enhance extra-

hepatic escape of the dye during these procedures, the agreement is remarkably good. Although these comparisons have been limited to Bromsulfalein there is no reason to suppose that rose bengal and indocyanine green would not prove equally reliable.

Of all the clearance materials at hand, BSP appears at present to be clearly superior. Rose bengal as obtained commercially is a mixture of several chromatographically separable components some of which appear to be less readily cleared than others. Though this defect is not important so long as hepatic extraction is determined, it may be troublesome. Composition varies from lot to lot with a resultant unpredictable irregularity in extraction and removal rate. The availability of I^{131} -labeled rose bengal (91, 213) simplifies analysis but does not compensate for the other difficulties. Indocyanine green is most attractive for many reasons. It is easily and accurately measured in the plasma; it is not conjugated, and it does not enter the urine nor move perceptibly from the plasma into any tissue other than the liver. Unfortunately, it is unstable on standing in aqueous solutions, and may prove unsuitable, therefore, for constant infusion. The chemical determination of Bromsulfalein offers certain difficulties, since it is difficult to remove the dye from the plasma proteins and to eliminate interfering materials present in the blank. It is possibly this factor that accounts for Sherlock's (273) finding [which others (48, 77, 78) have failed to confirm] that values for EHBF tended to be excessively high when plasma BSP concentrations were less than 1 mg per cent. Even a small error in the determination of arterial and hepatic venous concentrations may produce a large error in the A-V difference. In any case, interference by substances in the "blank" can be avoided for all practical purposes by appropriate dilution and use of the Beckman DU spectrophotometer.

A variety of other agents has been employed for determining EHBF but none has won wide acceptance. Galactose has been found to be metabolized by the liver alone with sufficient rapidity to permit accurate measurement of extraction and computation of hepatic removal at levels too low for significant urinary loss (293). Metabolic changes may interfere importantly, however. Alcohol has been suggested for use in the same manner but more recent work (191) has shown that it may be removed actively by tissues other than the liver. Finally the role of the liver as the major site of urea formation has been exploited in the measurement of hepatic blood flow. Urinary urea excretion has been taken as equal to the

rate of hepatic synthesis and divided by the amount of urea added to each milliliter of blood perfusing the liver (the hepatic venous-arterial urea concentration difference) to yield values for EHBF that agree with those obtained by the BSP method (217). The difficulties of analysis, correction for urinary delay, and maintenance of a steady state, militate against its routine use. Bromsulfalein appears to be relatively innocuous. Anaphylactic reactions are exceedingly rare (283) and occasional febrile responses appear to be due to contamination during preparation. Intense local inflammation follows extravasation of BSP into the tissues.

Single injection techniques. The hepatic "clearance" of any substance removed exclusively by the liver may be computed from the change in plasma concentration with time, following intravenous administration of a single dose. Here the word "clearance" has been used in a somewhat different sense than that outlined above. In renal physiology the term applies to the amount of any material excreted in the urine per minute relative to its concentration in each milliliter of plasma. This ratio has the dimensions of volume and is equivalent to the volume of plasma that would have been "cleared" completely of the substance in question, if it had been completely extracted from each milliliter. But the clearance (195) may also be computed from the falling plasma concentration following intravenous administration of a single dose provided *a*) the disappearance follows a simple exponential decay function:

$$C_t = C_0 e^{-kt}$$

(when C_0 is the initial concentration, C_t the concentration at time t , and k is the disappearance constant), and *b*) the plasma volume of distribution (V) is known. In this case clearance is equal to the product of V and k , since k is equal to the fraction of the volume that is completely cleared. The constant k is also often referred to, rather confusingly, as the "fractional clearance." In the estimation of hepatic blood flow by "single injection" it is necessary to find substances that are removed by the liver alone with almost 100 per cent efficiency, that are distributed within a determinable volume of distribution and that may be used for repeated determinations. If a radioisotope could be employed as such, or as a label for the ideal test material, changes in plasma radioactivity might be followed by external monitoring (over the thigh, for example), thus eliminating the objectionable features of the "con-

stant infusion" technique which includes repeated blood sampling, hepatic venous catheterization, and prolonged intravenous infusion.

The remarkable phagocytic activity of reticuloendothelial cells situated in the liver and splanchnic bed early suggested the possibility that particulate substances in colloidal suspension might be removed with sufficient efficiency to permit the development of single injection techniques (109, 272). Various agents in colloidal suspension including carbon, iron, gold, chromium phosphate, polyvinylpyrrolidone, and denatured plasma protein have been studied intensively by many workers (33, 109, 110, 272, 296, 316). In general it appears that phagocytic removal by the R-E cells within the liver and spleen depends upon particle size, "saturation," splanchnic blood flow, body temperature, and the obscure factors that determine preferential removal (55, 56, 316). Of these, particle size seems to be critical though difficult to define. Large particles (100 Å or larger) are taken up more actively than small ones; addition of plasma to the suspension prior to administration appears to enhance removal, possibly by increasing the bulk of small particles with a protein coating like that observed directly by Knisely *et al.* (185) prior to phagocytosis by Kupffer cells. The majority of studies in intact animals and man have involved the administration of P^{32} -labeled chromium phosphate, radioactive gold (Au^{198}) and heat-denatured plasma albumin labeled with I^{131} (33, 231, 242, 296). From 80 to 100 per cent of a single dose of each of these agents has been shown to accumulate in the liver and spleen and each yields a disappearance curve that can be resolved into two or more simple exponential functions. The values in plasma radioactivity do not usually fall to zero but tend to flatten into a straight line on semilogarithmic paper. This phenomenon has been attributed to the very slow removal of small particles which represent only a minute fraction of the dose. In practice the values obtained by extrapolating the "tail" of the curve back to zero time are subtracted from the initial figures to obtain a disappearance curve which is usually a single exponential that can be evaluated simply in terms of the disappearance half-time ($t_{1/2}$):

$$k = \frac{2.303 \log C_0 / .5C_0}{t_{1/2}} = \frac{.693}{t_{1/2}}$$

taking any value on the curve as C_0 and $t_{1/2}$ as the time required thereafter for the concentration, plotted semilogarithmically, to fall to half C_0 . The

value for k , i.e., the fractional clearance, is usually multiplied by the total plasma volume to yield a figure for EHBF. Colloidal chromium phosphate is difficult to prepare with a suitable range of particle size and is now little used. Radioactive gold and iodine are γ -emitters and their disappearance may be followed by external counting.

Perhaps the most serious difficulty with the single injection techniques lies in choosing the "volume of distribution" (V) to which the hepatic fractional clearance may be referred (108). Although the plasma volume is usually employed, a substantial fraction of the plasma volume within the splanchnic bed from which clearance has occurred cannot be included. The "volume" concerned is presumably one, too, in which admixture is instantaneous and throughout which the same concentration prevails at any moment. Attempts have been made to correct for "mixing time" by including a nondiffusible dye, like T-1824, with the test dose, but the corrections have proved relatively insignificant and have been deemed unnecessary. Attempts to compute V have proved less successful, especially following trauma or blood loss. Many workers use the volume of dilution calculated from the intercept at zero time obtained by extrapolation of the disappearance curve; others simply report values for k , or use the plasma volume less a fraction held in the splanchnic vessels. Another problem arises from the assumption that hepatic extraction is nearly complete. In early studies (296), values of 70 to 90 per cent were reported for colloidal Au^{198} , but more recently reported figures (231) range from 30 to 70 per cent, accounting perhaps for lower values for EHBF. Changes in the composition and properties of gold colloids commercially available may be responsible for this phenomenon. Although heat-denatured serum proteins labeled with I^{131} appear to be extracted very efficiently and, as an added advantage, are ultimately eliminated by normal metabolic processes, they have found little use in large part because I^{131} rose bengal and indocyanine green have proved more attractive (19, 183, 213). Both I^{131} rose bengal and indocyanine green disappear rapidly and exponentially from the blood and, since neither is lost in the urine nor taken up in significant quantity by extrahepatic tissues, both may be used to measure EHBF by the single injection technique. Nevertheless, uncertainty remains regarding the character of the volume of distribution from which the dyes disappear, the constancy and magnitude of extraction under all circumstances, and the part played by different mechanisms in deter-

mining the fractional clearance. Studies of BSP disappearance and of I^{131} rose bengal accumulation in the liver indicate the possibility of reflux, of interplay between coupled reservoirs and transfer systems, and of secondary derangements (e.g., saturation and competition) that may lead to error (45, 122, 177, 212, 312).

Dilution techniques. A third indirect approach to estimation of hepatic (or splanchnic) blood flow depends upon measurement of the dilution of a known quantity of some tracer within the hepatic circulation over an accurately measured time period. In essence, these procedures are adaptations of the Hamilton-Stewart method for the measurement of cardiac output and the Kety-Schmidt method for cerebral blood flow. For the first, which has been developed by Reichman and his associates (239), I^{131} -labeled human serum albumin (HSA) is injected into the spleen and the concentration curve followed either *a*) over the liver by external counting with approximate correction for background, or *b*) in hepatic venous outflow collected continuously at a constant rate with sampling at regular intervals. Analysis of the hepatic venous radioactivity curve (as in the analysis of pulmonary arterial concentrations for determination of cardiac output by the "dye method") yields a value for the average hepatic venous activity resulting from dilution of the injectate by splanchnic blood flow during the time chosen. The tracer injected into the spleen appears to travel as a compact "bolus" in the splenic venous blood though a fraction (significant in 20% of human subjects) may be left behind in the subcapsular tissues. Delayed entry into the splanchnic bed with "trailing" may result from slow uneven injection. The amount actually injected and diluted within the hepatic blood flow can be computed as the product of the radioactivity in the peripheral blood at equilibrium (taken at 10 min after injection) and the total blood volume determined separately. This quantity divided by the calculated "average hepatic venous radioactivity" yields a value for the total splanchnic outflow during the period of analysis. Uncertainties arising from recirculation, nonuniform mixing, determination of the quantity of I^{131} -HSA injected, and possible pooling, together with the difficulties involved in intrasplenic injection, limit the usefulness of this method. A similar procedure has yielded satisfactory results in the dog with injection of iodinated albumin and Cr^{51} (labeled erythrocytes) into the portal vein (278).

Application of the Kety-Schmidt technique has been suggested by a number of students (176, 288).

The average arterial-hepatic venous concentration difference during equilibration following the intravenous administration of substances freely diffusible throughout the liver and splanchnic bed, such as radioactive krypton, water labeled with deuterium or tritium, or 4-amino antipyrine, may be divided into the average hepatic venous concentration at equilibrium to obtain a value for splanchnic blood flow per unit mass of splanchnic tissue. Sapirstein (256) claims that the distribution within the body of such uniformly diffusible tracers shortly after injection is determined by the distribution of cardiac output and thus indicative of local flow as a fraction of output. According to this view, if radioactive potassium chloride is given to an experimental animal and allowed sufficient time to pass through the heart and lungs to the tissues of the body, and if the animal is killed before appreciable venous drainage and recirculation have occurred, the K^{42} content of the various organs can be used to evaluate the pattern of flow distribution. Periods of time ranging from 5 to 60 sec before death in the rat or 20 to 120 sec in the dog do not appear to affect the results (except for the brain), presumably because venous K^{42} content is much smaller than the arterial levels during these periods and because recirculation does not begin to contribute for about 30 sec. Although the drawbacks of such a procedure are obvious, interesting and helpful information may be obtainable by this means alone.

SPLANCHNIC BLOOD VOLUME AND TRANSIT TIME. The volume of blood within the splanchnic bed and the mean splanchnic circulation time may also be measured by an adaptation of the dilution methods (50, 94). Comparison and careful timing of the moment-to-moment changes in arterial and hepatic venous concentrations during the period of equilibration following injection of some substance which is confined to the vascular bed, such as I^{131} HSA, affords a measure of both the total quantity of tracer distributed within the splanchnic bed at equilibrium and the time required for passage from artery to the point of venous sampling. Thus the amount of tracer entering the splanchnic bed between its first appearance in the arterial blood (sampled from a brachial or femoral artery) and the point of equilibrium (defined as agreement between arterial and venous concentrations within the limits of analytical error over a period of 30 sec or longer) is equal to the product of the total splanchnic blood flow and the average arterial radioactivity (\bar{A}) during that period (t_{eq} in

sec). The amount leaving is the product of the blood flow and the average hepatic venous radioactivity (\bar{I}) at the same time. Since blood flow can be measured by the BSP method and average arterial and venous radioactivities can be obtained by "integrated sampling," the amount of tracer distributed within the splanchnic bed is easily determined following intravenous injection of I^{131} HSA and divided by the arterial concentration at equilibrium (A_{eq}) to yield a value for splanchnic blood volume:

$$SBV = \frac{(\bar{A} - \bar{V}) \times EHBV \times t_{eq}}{(A_{eq})}$$

where EHBV is expressed in milliliters of blood flow per second. Since splanchnic blood volume is equal to the product of the hepatic blood flow per second and the mean splanchnic circulation time (MCT) in seconds,

$$SBV = EHBV \times MCT$$

it follows,

$$MCT = \frac{(\bar{A} - \bar{V}) t_{eq}}{(A_{eq})}$$

It will be recognized that the Hamilton-Stewart and Kety-Schmidt methods alluded to above are applications of the same principle which has been treated at greater length mathematically by Stephenson and others (284, 315). [See also Chapters 18 and 19 of this *Handbook*.] Radioactive phosphate or chromium-labeled erythrocytes have been used to determine splanchnic red cell mass and erythrocyte circulation time (94). Any other relatively nondiffusible substance should yield equally reliable results, provided the major assumptions upon which the method is based are valid.

All the difficulties implicit in the measurement of hepatic blood flow pertain with equal force to the determination of the splanchnic blood volume. Of added importance is the assumption of "representative hepatic venous sampling," because the distribution of tracer within splanchnic blood flow varies from time to time during equilibration, appearing first in the hepatic arterial inflow and later in other parts of the bed. Thus the various splanchnic pathways must be represented within each outflow tract to an equivalent degree. In view of the anatomical arrangements and the data yielded by study of circulation time (see below) this assumption seems to be valid in normal man and animals. Local changes within the liver will certainly interfere and the effects of

streamlining (to be dealt with later) may also introduce inequalities by predisposing to predominance of splenic and gastrointestinal vascular routes within the left and right hepatic venous outflows, respectively. The fact that similar values are obtained with sampling from right and left lobes suggests that this possibility is not important, but further work is necessary to settle the matter. Uniform and diffused admixture of tracer throughout all the blood filling the splanchnic blood vessels must have been completed by the "equilibrium time." Since equilibration appears to be attained within 3 min or less, it seems most unlikely that volumes of blood held relatively motionless, in contact with but not actively a part of the circulating blood, are included in the final value. Tracer undoubtedly must find its way into the splenic pulp, but largely by diffusion rather than by active mixing, thus probably accounting for the lack of change in splanchnic blood volume (SBV) noted following splenectomy. For this reason the value should be referred to as the "circulating splanchnic blood volume." Although the term specifically indicates the volume of whole blood, the tracer usually employed (I^{131} HSA) is actually distributed within the plasma. Blood volume must therefore be computed from the estimated plasma volume and the arterial hematocrit. But the latter is not strictly applicable because the phenomena of "lamination" and "plasma skimming" result in a lower hematocrit in blood flowing through the capillaries than in arterial blood. The resulting error may be relatively large and must be borne in mind in interpreting shifts, particularly in association with a changing hematocrit. Simultaneous determinations of red cell mass and plasma volume should yield a more accurate estimate of the total volume, though measurement of the red cell mass is undoubtedly more seriously limited by the difficulty of complete admixture. Blood flow and volume must remain relatively constant during the period of determination—at least 10 min—to permit estimation of hepatic blood flow. Owing to the limits of accuracy imposed by the analytical procedures, blood flow must not be so large relative to volume as to minimize critically the difference between the mean values for arterial and hepatic venous radioactivities. Experiments with model systems in which the blue dye, T-1824, has been used have demonstrated the validity of the method provided flow per minute is not greater than three times the volume (63). A higher ratio may be compatible with sufficiently accurate measurement of the arterio-

venous difference when radioactive tracers are used (234). For the splanchnic bed the actual ratio is much lower, approximating unity under most circumstances. A more serious problem is loss of tracer en route either into the interstitial fluid or into collateral channels that bypass the liver. The first possibility is usually not very important. The second does not affect the measurement in normal subjects, but with cirrhosis and other conditions leading to the development of a collateral circulation measurement may be impossible. This consideration applies with equal force to evaluation of the "mean" circulation time.

An accurate analysis of the time required for blood to move through the splanchnic bed requires determination of tracer levels in artery and hepatic vein at 1-sec or 2-sec intervals owing to the rapidity of the change which must be followed (303). The development of satisfactory means of doing this by Wheeler (303), Tornvall (290), and their associates has made it possible to apply and to extend analyses of transit times worked out in the course of a study of urine formation (51). Since blood must be drawn through a catheter there is distortion of the concentration curve by the velocity differential produced by laminar flow (215, 274). This factor may be allowed for by sampling arterial and hepatic venous blood at the same rate through catheters having the same dimensions. Wheeler's collection technique involves the use of a 30-foot length of polyethylene tubing into which the blood is drawn together with droplets of mercury to break up the column of blood and to prevent streamlining. Since the tubing has a uniform calibre and since withdrawal is carefully timed, segments of tubing containing blood collected during successive 1-sec intervals can be heat sealed and cut off as separate "timed" segments for determination of I^{131} activity, after removal of the mercury droplets by centrifugation. Tornvall's device consists of a magazine of 50 U-shaped channels, each with a capacity of 3 ml, arranged in a carrier that automatically fills each channel in succession, at 1-sec to 2-sec intervals, as blood is withdrawn at a constant rate. It is possible to apply values so obtained in the construction of a frequency distribution of arterial-hepatic venous transit times. The effluent from a system of tubes draining a reservoir describes a frequency distribution of transit times from reservoir to sampling site when the reservoir tracer concentration is suddenly set at some arbitrary level (taken as 100%) at zero time. Changes in reservoir (or arterial) concentration are reflected in distortions in the effluent

(or venous) concentration curve which may be taken into account by sequential comparison and graphic integration. Although hepatic arterial and mesenteric vasculatures are undoubtedly characterized by markedly different mean circulation times, there is so much dispersion and overlap between these and other splanchnic beds that separation of specific populations has proved impossible. Nevertheless, the method affords a more precise indirect approach to an understanding of the intrasplanchnic distribution of flow and volume than any other now available.

NORMAL PARAMETERS OF THE HEPATIC CIRCULATION

Although methodology is now far-advanced, a reliable quantitative description of the hepatic and splanchnic circulation at rest in man and experimental animals is still a major desideratum. Uncertainty results from all the technical difficulties already noted. In addition, the control or "resting state" is extremely difficult to define and is perhaps, like the "normal," a relatively meaningless concept. The splanchnic circulation (hence, the hepatic outflow) serves at one and the same time the demands of viscera engaged in a diversity of metabolic activities and the needs of the cardiovascular system as a whole. The establishment of a steady state referable to each of these factors would be almost impossible and, in any case, of limited applicability. For this reason it has seemed preferable to abstract suitable "control" approximations from the literature and to consider these as the basis for a reasonable appraisal of what may be characterized as the "reference state."

Hepatic Blood Flow

Of necessity, data obtained in studies of man and dog must dominate the picture. Although the hepatic circulation has been investigated extensively in the cat, rat, mouse, rabbit, and other species, the information obtained has been largely qualitative; of considerable importance in elucidating physiologic and pathologic adjustments, of but inferential value quantitatively. Systematic exploration of the field of comparative physiology with the methods at hand would be most rewarding. In both man and dog, the figures for hepatic blood flow, portal venous and sinusoidal pressures, and splanchnic blood volume range widely. In 91 apparently normal fasting human subjects, studied resting in recumbency, the BSP

method yielded a mean value of $1530 \pm (\text{SD}) 300$ ml per min (48), which appears to be fairly representative [and certainly not differing significantly from the figures published by other workers using the same or other methods (33, 78, 231, 242, 273, 296)]. The wide range observed suggests a considerable variation in flow that is also evident (though by no means to the same extent) during the course of a single study in the same subject. For the dog, the values obtained by different workers differ much more significantly (37, 90, 129, 232, 275, 282). To a large extent the disagreement may be ascribed to differences in preparation, anesthesia, and surgical manipulation. Anesthesia appears to be particularly difficult to control, since it may be associated with a varying degree of hypercapnia with resultant splanchnic vasoconstriction. Light barbiturate anesthesia appears to produce no change in splanchnic hemodynamics in man so long as the plasma carbon dioxide tension is kept constant (123). Artificial respiration with various mechanical devices predisposes to hypercapnia in man and it may be assumed that this is also true of the dog. Hence, it seems reasonable to accept the mean values for EHBF obtained in unanesthetized dogs by Pratt (232), Bollman (37), Fisher (129), and their co-workers of 43.6 ml, 42.5 ml, and 45 ml per kg body wt per min, respectively, as the best available estimates. As in man, variance is relatively large (in Fisher's series, for example, the standard deviation was ± 9.3 ml/kg body wt/min) and a similar variation is observed during the course of a single study. The values for EHBF are not correlated with body size in man as they are in the dog, presumably because the range of variation in body size in man is so much less than in the dog and because a correlation may be obscured by other factors responsible for variance in "resting" EHBF. Dobson & Jones (110) have reported mean values for hepatic blood flow (chromic phosphate method) in the unanesthetized rabbit, rat, mouse (0.74, 1.2, and 1.4 ml/ml liver/min, respectively) in rough agreement with those for man and dog. Similar values have been reported also, in terms of body weight, for sheep and cattle (138, 260).

Splanchnic Vascular Pressures and Resistances

The figures available for arterial and venous pressures and for pressure differentials in different species also indicate close similarities though a definitive and systematic investigation remains to be done. In every series the values range so widely that inter-

species differences are apparently insignificant (17, 32, 76, 135, 244, 286, 314). This variation may be explained largely by the technical difficulty of establishing strictly comparable "zero reference planes," states of "resting normality," and laboratory conditions. Nevertheless, mean arterial pressure may be taken as approximately 100 mm Hg in both man and dog, portal venous pressure as 10 mm Hg, and central (or atrial) venous pressure as 0. Since portal and wedged hepatic venous pressure in dog and man behave in the same way and attain the same levels, the value for sinusoidal pressure of 8.5 mm Hg computed for the dog by Friedman & Weiner (135) as the midpoint between wedged hepatic and wedged portal venous pressures may be accepted also for man. The pressure gradients therefore are 90 mm Hg between artery and portal vein, 91.5 between hepatic artery and sinusoids, 1.5 between portal vein and sinusoids, and 8.5 between sinusoids and the right heart.

The resistances that determine these drops in pressure between the arteries and veins can be evaluated only when the distribution of blood flow is known. Exact figures are not available but most workers (though not all) tend to accept the view that hepatic arterial inflow is approximately one-half portal venous inflow (132). If this is the case and if resistances may be computed as the ratio between pressure drop (given above) and flow per second (1530 ml in man and 550 ml in the dog) multiplied by a factor—1332—to obtain figures in absolute units (dynes cm^{-5} sec), the following values for resistances within the splanchnic bed would obtain in man and dog (10 kg):

| | <i>Man</i> | <i>Dog</i> |
|---------------------------------------------------------|------------|------------|
| Arterial sinusoidal (hepatic arteriolar— R_1) | 14,630 | 48,750 |
| Arterial portal venous (splanchnic arteriolar— R_2) | 7200 | 24,000 |
| Portal venous sinusoidal (portal venular— R_3) | 120 | 400 |
| Sinusoidal inferior vena cava (post-sinusoidal— R_4) | 450 | 1510 |

The interrelationship between resistances is complicated by the fact that the splanchnic circulation consists of a combination of resistances both in series and in parallel (fig. 1). The computation of any component requires a precise information regarding the distribution of total blood flow as well as pressure gradients. Any attempt to infer behavior of a given resistance from values for the pressure

FIG. 1. The hepatic and splanchnic circuits. The vascular resistances in the splanchnic bed (A) are shown here in diagrammatic form (B). The resistances indicated are the determinants of sinusoidal and portal venous pressures and of flows through the portal vein and hepatic artery. In addition to the hepatic arteriolar resistance (R_1), colic, mesenteric, pancreatic, gastric, and splenic arteriolar (R_2), portal venular (R_3) and post-sinusoidal (R_4) resistances, a fifth resistance lying in direct communication between the portal vein and inferior vena cava (the collateral resistance) is shown as a dotted line. It may be seen that the resistance pattern resembles that of the Wheatstone bridge, though the electrical analogy must not be taken too literally. The total splanchnic resistance (R_T) may be expressed (44) in terms of its constituent resistances as follows (omitting the collateral resistance):

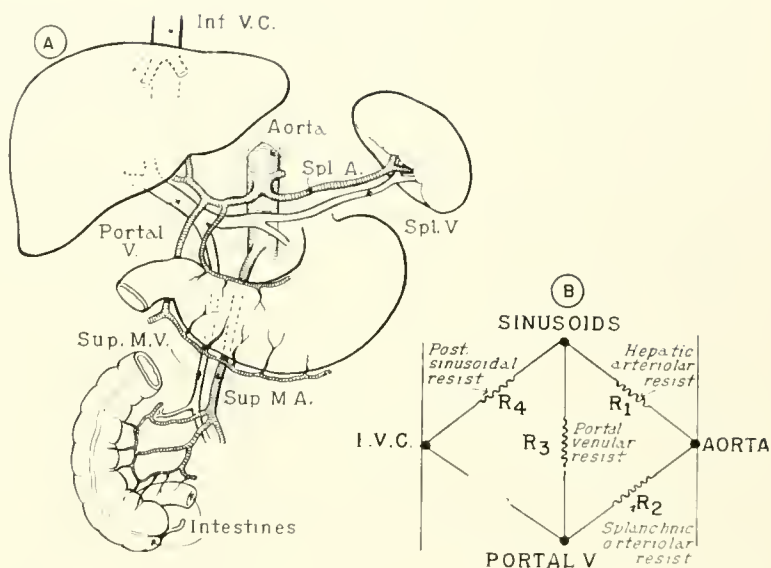
$$R_T = \frac{R_1 R_2 + R_1 R_3}{R_1 + R_2 + R_3} + R_4$$

[Reprinted from (43) with permission of the publishers.]

gradient alone is fraught with the danger of serious error. If the values above are correct, it is evident that the resistance to outflow from the liver and the portal venous bed is a fraction of inflow resistance. It may be inferred therefrom that relatively small absolute changes in R_3 and R_4 would influence portal venous and sinusoidal pressure markedly, and in doing so, affect the volume of blood distending the portal and hepatic vasculature.

Splanchnic Blood Volume

The balance between input and outlet resistances and the "capacity" of the vasculature together presumably determine splanchnic blood volume and the pressures under which the vessels are distended. The relative contribution of each is difficult to assess not only during change but also in the basal reference state. The total circulating splanchnic blood volume (regional dilution method) in both dog and man at rest amounts to approximately 20 per cent of the total blood volume, within a wide range attributable both to technical and physiologic factors (43, 44, 50, 106, 175, 181). Of this, the bulk appears to be held within the large veins (for details see below), though an important moiety is lodged within the sinusoids of the liver and the spleen. The intrinsic capacity of this variegated system at any pressure thus depends upon the elasticity of muscular veins and the counter-



forces operating to compress or distend the intra-abdominal viscera and their vasculatures.

Muscular contraction may quickly modify the former, whereas the introduction of food, water, and air into the gastrointestinal tract and the movement of fluid across the cell walls may change the latter very slowly. It is difficult, under the circumstances, to establish satisfactory reproducible control values. Moreover, the pressures acting in the different parts of the bed are effective in proportion to diameter, in accord with Laplace's law (70) so that a much greater pressure rise is necessary to increase sinusoidal volume than to produce the same increment in venous volume. Insufficient data are available to permit quantitative evaluation of this factor in different regions and to give proper importance to venous and capillary pressure levels.

The cross-sectional distribution of the vessels, containing the blood, figures importantly not only in determining the average distensibility but also in fixing the average hematocrit and the composition of the splanchnic blood volume. Lamination of flowing blood results in a lower hematocrit in capillaries than in large vessels, owing to the relatively large volume of plasma in the layer immediately adjacent to the vessel wall. Sequestration of blood with sluggish turnover may lead to accumulation of red cells, however, and to a higher hematocrit than in the large vessels. The hematocrit of the circulating

splanchnic blood volume of the dog has been proved to average 79.4 ± 8.9 per cent of the simultaneously determined arterial hematocrit (94). Splenectomy does not significantly affect the value, presumably because the tracer is not dispersed throughout the spleen. Since circulating SBV is computed on the basis of the arterial hematocrit it is evident that the value is overestimated by the extent to which the splanchnic hematocrit differs from the arterial and underestimated by failure to include stagnant splenic blood. Nevertheless, the magnitude of the value indicates at once that the splanchnic reservoir can contribute significantly in systemic circulatory homeostasis by mobilizing a large volume of blood to repair deficits in the peripheral circulating volume or by expanding to accommodate an excess that might threaten cardiac stability.

At present, methodology undoubtedly figures most prominently as a cause for contemporary figures denoting hepatic circulatory variance. Active vascular adjustments must also play an important role in producing the variability observed in measurements of flows, pressures, and volumes at "rest" in view of the abundant evidence of muscular tissue and muscular activity in influencing flow and volume. The same fundamental mechanisms are involved in the circulatory changes observed during "acute" responses to various stimuli and stresses. Alterations in vascular dimensions and elastic properties and in hemodynamic patterns arise primarily from the varied interplay of vasoconstriction, closure, or collapse of vessels, and rearrangement of vascular pathways, but numerous additional extraneous factors exert a vital modifying, integrating, and directive influence. Among the latter it is necessary to consider neural mechanisms, humoral agents, and external physical forces that are imposed by abdominal muscular contraction, tissue tension, gravity, respiratory movements, and the like.

PRIMARY DETERMINANTS OF HEPATIC BLOOD FLOW AND VOLUME

Cross Section

Since blood flow and volume are functions not only of the driving and distending pressures but also of the dimensions of a vasculature, splanchnic vascular anatomy may be considered an immediate determinant of hepatic hemodynamics. Structure, as such, however, is not constant in its physiologic

implications nor is it particularly helpful in indicating the control reference state because death and dissection result in disarrangement of the delicate balances that depend upon tissue turgor and muscle contraction. Nevertheless, anatomic data may help in suggesting the points at which resistance to flow should be most marked. Mall's (206) careful measurements of the dimensions and numbers of vessels within the liver and splanchnic bed can still be used, more than half a century after their publication, as a basis for computing sites of resistance. Assuming that each successive category of vessels gives rise to a new system of resisting conduits in parallel, the cross section of each conduit progressively diminishing to the level of the capillaries; the frictional resistances to flow at each level may be computed from Poiseuille's law of fluid flow through capillary vessels in parallel as follows:

$$\frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} \dots$$

where R_T is the total resistance imposed by any category of parallel branches and R_1, R_2, R_3, \dots are the resistances imposed by each constituent branch. Since resistance in each branch varies inversely as the fourth power of its radius (r) and directly as its length (l) and the viscosity (η) of the perfusate:

$$\frac{1}{R_T} = \left(\frac{r^4}{\eta l}\right)_1 + \left(\frac{r^4}{\eta l}\right)_2 + \left(\frac{r^4}{\eta l}\right)_3 \dots$$

and if the average radius (\bar{r}) is used:

$$\frac{1}{R_T} = \frac{n\bar{r}^4}{\eta l} \text{ or } R_T = \frac{\eta l}{n\bar{r}^4}$$

where n is the number of vessels in each category. Changes in the values for viscosity and length contribute negligibly to the change in total resistance as the vessels narrow and increase in number. The values presented by Mall for the number of branches and for the average cross section at each level indicate that $(1/n\bar{r}^4)$ reaches a maximum in the smallest arterial branches (or arterioles) in the liver, spleen, stomach, and intestines. It may be inferred, therefore, that arteriolar resistance plays a preponderant role in determining splanchnic and hepatic inflow. Beyond this point in both the portal venous and hepatic venous systems, values for $(1/n\bar{r}^4)$ fall to very low figures though slight increases do occur at the level of the smallest portal venular branches and the sinusoids. No evidence of a significant postsinusoidal resistance may be adduced from these data, though

the wedged hepatic venous-central venous pressure differential gives proof to its operation while the thick throttling musculature of the small hepatic veins (in the dog, at least) suggests a mechanism for its production. The musculature of the arterioles also indicates an apparently adequate basis for variation noted in intrahepatic or splanchnic resistances and blood flows. Nevertheless, other factors enter the equation and under certain circumstances contribute effectively in changing the total vascular cross section independently of vasomotor activity.

Collapse of vessels secondary to changes in transmural pressure may result in the redistribution of resistances and in the reduction of the number and diameter of the units perfused at any level. Much work in recent years (149, 162, 226, 307) indicates that perfusing pressure and blood flow are linearly correlated only above 20 to 40 mm Hg in the maximally dilated vascular beds of the isolated hind limb of the dog. At lower pressures the pressure-flow curve is sigmoid with a positive intercept on the pressure axis. Green and his associates (162) have suggested that vascular compliance may produce the convexity to the base and the positive pressure intercept at zero flow, the perfused vessels decreasing in cross section and number as the distending pressures are lowered with increasing resistance in consequence. This phenomenon has been extensively studied by Burton and his associates (70-72) who attribute it to an inherent vascular instability that develops as the product of the intraluminal pressure and the radius falls below the "tension" in the wall. At this point, that of "critical closing pressure," collapse occurs and the vessel "shuts down." The mural tension is attributed to the interplay of elastic tension or tissue resistance to stretch, active tension generated by muscular contraction, and interfacial tension arising from the surface forces between blood and the "unwetttable" intima. A significant correlation noted between critical closing pressure and resistance to flow in various preparations (including the perfused ear of the rabbit, intact dogs with extracorporeal circulation, the human hand during changes in transmural pressure) has been interpreted as evidence that the arterioles are chiefly concerned. The linear relationship between high pressures and flows observed by Whittaker & Winton (307), Pappenheimer & Maes (226), and others (70, 71) indicates nondistensibility of the resistance vessels and appears to be a result of maximal dilatation in their experiments. Levy (194), Folkow & Lofving (131), and others (166) have shown that the resistance vessels are freely

distensible over a wide range of pressures produced by equal increments in both arterial and venous pressures, less so when arterial pressure alone is raised and more obviously with a rise in venous pressure alone; provided the bed is denervated and before local adjustments obtrude. Thus resistance to flow through an extremity may be diminished by raising the intravascular pressure and increased by lowering it.

Studies by Brauer *et al.* (57), Trapold (292), and Selkurt *et al.* (269) indicate that critical closing pressures may also be defined for the vasculatures of the liver and intestines. All have used isolated denervated tissues perfused *in vitro* over a wide range of pressures. Brauer *et al.* (57) obtained a sigmoid relationship between perfusion pressure and flow through the isolated rat liver perfused via the portal vein alone. They found an increment in resistance below pressures of 5 to 10 mm Hg apparently attributable to closure of a significant proportion of vessels that occurred in association with impairment in bile formation. Pressure-flow relationships were evaluated by Trapold (292) and Selkurt *et al.* (269) in the vessels of isolated loops of small intestine. Both observed linearity between 60 and 150 mm Hg, convexity to the pressure axis at about 60 mm Hg or lower, and a tendency for flattening at higher pressures. The zero flow intercept on the pressure axis was 16 mm Hg. They interpreted these findings as evidence of "critical closing" at low pressures and of distension with diminishing resistance as pressure was increased. All three groups noted the changes in critical closing pressure (rising with vasoconstriction and falling with dilatation) observed by Burton and his co-workers (70-72) during vasomotor activity produced by drugs and anoxia, and attributed by them to a change in "active tension." In normally innervated beds or in carefully prepared tissues, however, the correlation between critical closing pressure and the level of vasomotor tone did not appear to be readily demonstrable and free distensibility was not apparent (250). Indeed, additional evidence suggests that stretch of the vessel wall by a rise in intravascular or transmural pressure may actually elicit a reactive contraction of the smooth muscle, that prevents distension and that may even reduce cross section.

The possibility that intraluminal tension might determine vascular tone in this manner was raised by W. M. Bayliss in 1902 as an explanation for his observations that transient occlusion of the femoral artery was followed immediately in the denervated limb by hyperemia, and that a sharp rise in intraluminal pressure elicited an increase in "tone" of

isolated arterial segments. Owing to the questionable application of these observations to the situation in intact animals and the uncertain role of local vasoactive materials, the "myogenic theory of tone" was not readily accepted, but recent work by Folkow and others appears to have put it upon a sounder basis. Folkow & Lofving (131) worked with the denervated hind limb, skin, and mesenteric arterial bed in anesthetized cats, dogs, and rabbits. They found that lowering the arterial pressure for as short a period as 3 to 5 sec by arterial or aortic occlusion produced dilation, whereas raising the pressure by bilateral carotid occlusion for 20 to 60 sec elicited a vasoconstriction. Neither anoxia nor hypercapnia altered the response. Denervation apparently eliminated neither vascular tone nor responsiveness to vasoactive drugs such as acetylcholine, epinephrine, norepinephrine, serotonin, vasopressin, and angiotensin. From these results and from direct study of isolated arteries and minute blood vessels Folkow concluded that "vascular tone" is created by a rhythmic unsynchronized activity of the smooth muscle of the resistance vessels. Conclusive demonstration of myogenic autoregulation within the mesenteric vasculature has proved somewhat difficult, though Johnson (180) has been successful in finding it in 21 of 26 experiments. The response, he observed, was not eliminated by infusion of enough procaine to block a possible local autonomic reflex arc and did not appear to depend upon a change in tissue fluid content, oxygen consumption, or lactic acid production. The use of a suitable perfusion system and enough time to permit recovery from surgery, venous cannulation, and denervation may have been important in Johnson's success in demonstrating the phenomenon. Study of pressure-flow relationships in the portal venous drainage tract has been less clear cut in showing evidence of myogenic maintenance of tone. Although the data obtained by Riecker (250) with perfusion of the canine liver via the portal vein *in situ* are not marred by the effects of the trauma and disorganization, inevitable during excision and study *in vitro*, they exhibit considerable variance; opposing, on the one hand, the view that the porto-hepatic vasculature is a simple, passive elastic system and failing to support, on the other hand, intrinsic control of vascular cross section.

Although the data indicate that closure by collapse may occur in the hepatic and splanchnic vasculature, the role of a definite critical closing pressure remains uncertain. Confusion arises particularly in connection with the character of closure. According

to the myogenic theory, the "unstretched radius" is reached after the complete contraction of elastic recoil and is therefore zero. In this view, closure consists in a concentric constriction, but it may also be regarded as collapse to form a closed slit from some finite value for the unstretched radius. Since critical closing has apparently escaped direct observation, it is impossible to say which, if either, state obtains. The fact (70) that the pressure at which closure occurs does not differ from that at which the vessels re-expand (critical opening pressure) favors the first, at least so far as the resistance vessels are concerned. There is ample evidence that the critical opening pressure for the large veins greatly exceeds their critical closing pressure. A response similar to that of the large veins—and slit formation on closure—seems more likely also at the level of the tenuous venular channels and capillaries and at arteriovenous communications. However, the liver plates must move with expansion or deflation of the sinusoids to impose special plastic properties quite unlike those characteristic of other capillary nets. Critical closing pressures in the depth of a lobe probably differ markedly from those characteristics of sinusoids close to the surface not only because deformation must affect the periphery more easily but also because the distance from the afferent vessels is shorter in the central regions. No matter what the mechanism of closure may be, it effectively changes resistance to flow by reducing the vascular cross section. In addition, the distribution of collapse may affect the resistance by altering the mean length of the resisting circuits.

Path Length and Distributional Pattern

Resistance is directly related to path length and though the length of the conduit contributes much less to frictional loss of the energy head at any level than does the radius, it figures importantly in the total resistance from artery to vein. Arteriovenous or veno-venous shunting is the most obvious means of shortening the vascular bed. Arteriovenous anastomoses (A-V) occur prominently in the wall of the stomach (22, 39) and may be operative elsewhere in the gastrointestinal tract, but there is little evidence that they are significant hemodynamically. Even when the capillaries of the perfused stomach are completely blocked with starch granules, no more than 5 per cent of the total flow passes through the A-V anastomosis. Few or none are demonstrable in the liver though Prinzmetal *et al.* (233) have re-

ported that glass spheres up to $180\ \mu$ in diameter may be recovered from hepatic venous effluent following injection into the portal vein. In contrast, Gordon *et al.* (150) obtained much smaller values with a method based upon the established relationship between perfusate surface tension, minimal perfusing pressures, and the largest radius in a system of tubes. They found that portal to hepatic vein "anastomoses" did not exceed $24\ \mu$ in diameter and hepatic A-V anastomosis ranged from 18 to $26\ \mu$ in the rat and rabbit. The former are probably the hepatic sinusoids proper; the latter, the A-V anastomosis reported by Wakim & Mann (299) and Seneviratne (270). With respect to the data obtained with glass beads, they note that the method "yields remarkable results in that every organ investigated by this means has been shown to have very large A-V anastomoses." Whatever the merits of this dispute, vascular anastomoses do not seem to play a large part in determining hepatic hemodynamics. Possibly they operate in establishing distributional patterns of flow but even here cross section and path length per se appear to be more important.

The characteristic patterns of the pathways by which blood travels through the capillary beds within the hepatic and splanchnic vasculature are imperfectly understood. There is now fairly general agreement that capillaries themselves possess no intrinsic capacity for contractility or for autoregulation of flow and volume within them. Chambers & Zweifach (82) claim that capillary nets are characterized by continuously active and well-marked "thoroughfare channels" or "A-V capillaries," which pass more or less directly from the arterioles to the draining veins and from which the bulk of the capillaries take origin. According to these workers, the proximal portion of the central channel is encircled by muscle cells and is to be regarded as a junctional arteriole or "met-arteriole" which gives rise to even less well-muscled "precapillary" vessels or "precapillary sphincters" controlling inflow cross section. This arrangement has been described with what seems complete validity in the mesenteries (82, 317) but does not seem to be typical of capillary nets in other tissues (154) [see also Chapter 27 of this volume]. Active, more or less rhythmic, alternating dilatation and contraction or so-called "vasomotion" has also been observed in the terminal arterioles by time-lapse photography. Not all workers have been successful in convincing themselves of the validity of vasomotion but all seem in agreement regarding the phenomenon of "intermittency" or transient nonperfusion of a frac-

tion of any given capillary bed. Flow ceases or capillaries empty completely and remain so for a time, then flow resumes without apparent cause. During hyperemia nearly every capillary visualized will be active. Ischemia seems to reduce the number of active capillaries as well as to diminish flow through those remaining in function. This phenomenon has been repeatedly observed (185, 225, 270, 299, 317) in the hepatic sinusoidal system as well as in the capillary beds of the mesenteric distribution, the pancreas, and the spleen. Of course, the capillaries accessible to direct visualization are an infinitesimal fraction of the total and probably not a representative or random sampling. Intermittency probably occurs during normal life and may be involved in altering actively the total resistance to flow, but it seems not unlikely that it is an expression of capillary instability resulting from a critical reduction in distending pressures by "path-length resistance."

Innumerable routes of various lengths may be followed by the blood from the aorta to the hepatic vein. On the arterial side, the gastric, mesenteric, and colic vessels are particularly long and variable with interconnection by arcades that may serve to equalize input pressures and flows. The hepatic and splenic arteries are shorter and more direct but path length varies nonetheless because hilar entry results in short routes in the more central regions and longer ones by way of the parenchymal tissues situated at the periphery. The same configuration applies to the hepatic portal inflow tract but here the low pressure head and the minimal cross-sectional resistance appear to confer greater importance upon path length as a determinant of energy loss. Daniel & Prichard (101, 102) claim that portal blood does not always perfuse the entire liver for this reason. They used rapid serial angiography as a means of assessing distribution of flow following injection of Thorotrast into a mesenteric vein in cats, rabbits, guinea pigs, pigs, and goats. The contrast medium was usually found to move freely into the portal vein and its branches, then into the sinusoids, opacifying the organ diffusely with sharp definition of its profile, and finally into the hepatic veins and inferior vena cava. In a few rats and kittens, a "restricted intra-hepatic circulation" was demonstrable with failure of the Thorotrast to fill the outermost ramifications of the portal vein, with an irregular and patchy opacification limited to the central tissues and with filling of only those segments of the hepatic veins which lie relatively near the hilum. This phenomenon could be induced by stimulation of the hepatic nerves and by

partial hepatectomy suggesting the possibility that neurovascular mechanism is involved. Although the contrast substance appeared to move more rapidly into the hepatic veins with the "restricted" pattern, no evidence of veno-venous shunting could be adduced. Circulation time estimated in this way is not a reliable guide to the actual velocity of the blood. Any reduction in the volume of blood held in the vessels would reduce the transit time without necessarily affecting flow. The rise and fall of Thorotrast concentration in the entering blood must also be taken into account as well as the extent of dilution by arteriolar inflow. Blood flow was not measured and it is impossible to say whether the alteration in portal inflow was associated with a compensatory change in hepatic arteriolar resistance. The phenomenon suggests that the peripheral sinusoids which can be examined directly and in which intermittency has been observed may be peculiarly susceptible to shifts in the pattern of perfusion. It is probable that the same considerations are applicable to intermittency in mesenteric and splenic vessels. Determination of the distribution of circulation (or transit) times across the splanchnic bed in the dog (303) indicates that separate populations of path lengths (e.g., hepatic arterial, splenic, and mesenteric channels) overlap markedly, each possessing very short and very long routes. Hence the effect of special distribution patterns within any one circuit (such as the hepatic) would have little detectable influence upon the composition of draining blood. The fact that BSP transfer remains relatively constant over a wide range of flow suggests that parenchymal cells are uniformly perfused under most circumstances (305).

Viscosity

The equation of vascular resistance with the number, cross section, and length of the arterioles alone implies that blood flows freely without turbulence as an ideal Newtonian fluid in accord with Poiseuille's law. In reality, of course, blood is a highly complex and heterogenous suspension of red cells in a colloidal solution of proteins. Much evidence indicates that its viscosity is altered by the character of the conduit, by perfusing pressure, and by flow (202). Although there is little reason to believe that critical velocities are frequently exceeded in any portion of the splanchnic vasculature, turbulence may be induced by respiratory and body movements which check the flow of blood and give rise to transient vortices and eddies. Turbulence may also arise during arterial pulsation

with a tendency for the blood to move backward, even in the capillaries, during diastole. Laminar flow results in inward movement of red cells and accumulation about the axis presumably owing to nonuniform distribution of the shearing force across the lumen of the vessel and to shear rate dependence of plasma viscosity (202, 301). However, this process appears to be inconsistent, so that turbulence of a sort always occurs and produces a "mixed flow." Both the cell-free zone of plasma and the high velocity differential next to the vessel walls permit "slippage" and result in a lower than expected viscosity in vessels of small diameters where the volume of "plasma-lining" is proportionately larger. From this layer is derived the plasma which enters capillaries by the process of plasma-skimming observed in the hepatic sinusoids and mesenteric capillaries by Knisely (185) and others (225, 270, 299). Consequently, the blood perfusing capillaries may vary widely in viscosity as well as hematocrit with resultant irregularities that are not readily resolved in hemodynamic analysis. The development of turbulence under various circumstances and the effects of anomalous viscosity complicate matters still more.

With turbulence, a more complete admixture of blood results. Thus the blood entering the arteries from the heart has undergone a thorough stirring and may be regarded as having a relatively uniform composition. Within the large veins, lamination results in an unequal mixing of converging streams of varying composition so that "representative sampling" from the inferior vena cava, for example, may be difficult or impossible. Similarly, "layering" may occur in the portal vein and give rise to nonuniform distribution within the liver, of blood coming from the gastrointestinal, pancreatic, and splenic veins. This possibility, first broached by Glenard in 1890, was given experimental support by studies of S  r  g  , who found that India ink injected into the splenic vein of dogs was carried preferentially to the left lobe of the liver. Later, Bartlett *et al.* (24) found that absorption of copper sulfate from the stomach and duodenum of dogs resulted in deposition preponderantly in the left lobe and that absorption from the ileum led to deposition in the right. Copher & Dick (95) observed "stream lines" in the canine portal vein directly with transillumination following injection of trypan blue into various portal tributaries. Perhaps the most convincing evidence of "bilateral flow of portal flow" was reported in 1945 by Hahn *et al.* (168). These workers injected radioactive phosphorus as orthophosphate into the splenic vein, mesenteric

vein, or jugular vein of dogs after placing loose ligatures around the portal vein, hepatic artery, and inferior vena cava. After approximately 3 sec the ligatures were tied and the liver removed immediately, transverse sections cut and "wet ashed," and radioactivity determined on the measured aliquots. After injection into the jugular vein, the radioactivity was found uniformly distributed through the liver from right to left. Three-quarters of the radioactivity appeared in the left side of the liver after injection into the splenic vein, and approximately the same proportion appeared on the opposite side after injection into the mesenteric vein. Each observation was made but once, under anesthesia, with the abdomen open and after extensive manipulation of the viscera. Hence, application of these data to the situation in man is most uncertain. Nonetheless, there has been a tendency among clinicians to explain the distribution of pathology in human hepatic disease on this basis.

Barnett & Cochrane (23) have recently pointed out the importance of species and individual anatomic peculiarities in altering lamination. Experiments on a model system proved helpful in evaluating these effects of branching and convergence of tributaries upon the distribution of streamlines at varying rates of flow with different perfusates. For branches like those at the hilum of the liver, they found that the chance that particles in the major trunk "remote from the branch would pass into it are greater with increasing viscosity and decreasing width of the branch," the angle of outflow having little significance at the rates of flow usually prevailing. Thus, for a fluid like blood, small branches would seem likely to be perfused by a fairly representative sample of the total inflow. "Moreover, the manner of formation of the portal vein is important. Where it is formed by a tributary joining a straight main vein (*V*) particles are more likely to pass across the portal vein when the rate of flow in the tributary is large and its diameter small. The converse is true where the portal vein is formed by the symmetrical union (*V*) of a major and minor tributary, unless the rate of flow in the minor tributary is very high. In both types of junction more crossing-over of the streams occurs when the angle of union is larger than when it is acute."

Although these considerations are of importance it is probable that local movements of vessels are of even greater significance in determining the extent to which the blood streams commingle in the portal vein in the intact animal and man. In the anesthetized dog secured in the dorsirecumbent position, with the abdomen open and respiratory movements mini-

mized, it is not surprising that lamination may be detected in the inferior vena cava (132). And even under these circumstances Cole and his associates (89) found that I^{131} -labeled rose bengal was uniformly distributed in the liver following injection into four of the different divisions of the portal vein draining the spleen, small intestine, cecum, and colon of the dog. In intact man and dog it has proved a much more elusive phenomenon. Portal venography by intrasplenic injection of contrast substance has usually failed to show much evidence of "physiological bilaterality." Streamlining or a filling defect in the shadow of the portal vein at the point of entry of the superior mesenteric vein attributable to lateral filling by radio-lucent blood from the mesenteric vein has been reported (15, 116) but it is by no means a constant, or even a frequent observation. Indeed, Patrassi and his colleagues (229) claim that injection of contrast substances into the spleen tends rather to make the right lobe more opaque than the left. In addition, they found no significant difference between the transit times from spleen to each of the two lobes when small amounts of sodium para-aminohippurate or red blood cells labeled with radioactive phosphorus were injected into the spleen of human subjects. Similar studies in dogs yielded the same results. Incomplete portal venous admixture may therefore be regarded as a potential but unlikely result of the viscous properties of blood. Hemodynamically it is important chiefly with respect to the movement of red cells and variation of hematocrit within the splanchnic and hepatic vessels.

Volume and Distensibility

The potential volume of the vasculature which houses the "circulating blood" of the splanchnic bed may be analyzed dimensionally with the data published by Mall (206) which have already been employed in determining the major points of vascular resistance. Using data for the length of vessels in the mesenteric circuit from the work of Schleier (261), and estimates of vascular lengths in the liver, the total volume of each vascular category may be computed as for cylinders. The internal volume of hepatic and mesenteric arterial inflow tract in a dog of "medium size" (liver weight—ca. 175 g) was found by this means to amount to 4.1 ml; the mesenteric and portal venous systems, 42.6 ml; the sinusoids, 32.3 ml; and the hepatic venous outflow tract, 41.1 ml. Thus the arteries accounted for some 3.3 per cent of the total, the sinusoids and mesenteric capil-

laries for 27.5 per cent, and the veins for the remainder or 69.2 per cent. Assuming that the gastric, colic, and pancreatic vessels hold no more than twice the amount in the mesenteric vessels, and omitting the spleen, the splanchnic bed in Mall's "dog" held a total of 153 ml or 28.5 per cent of the blood volume of an animal weighing 7 kg (taking the liver weight and blood volume as 2.5 per cent and 7.7 per cent, respectively, of body weight). Since the total values compare favorably with those yielded by other methods, the figures indicating distribution of volumes may be regarded as equally valid in pointing to a predominance of the veins in determining the volume of blood contained within the liver and the splanchnic bed at rest. As noted above, the veins of the splanchnic bed are generously supplied with muscle and it may be surmised that their capacity is subject to change by venomotor activity.

The obvious constriction or dilatation of veins—including those of the splanchnic vasculatures—in response to chilling, tapping, warming, or various injurious manipulations indicates clearly the ability of the venous musculature to alter the calibre and length of the veins (132). The mechanisms by which venous smooth muscle effects these changes, the integration and function of circular, spiral, and longitudinal fibers in different veins, and the patterns of contraction and relaxation are most obscure. Zweifach (317) and others (132) have reported spontaneous "intermittent activity" not only in the arteries and arterioles of the mesenteries but also in the small venules, with cycles of alternate filling and emptying that appear to be irregular, unpredictable, and independent of the innervation. Similar fluctuations have been observed by Knisely and his associates (185) at the level of the central veins and sinusoids in the liver, presumably secondary to activity of the well-muscled sublobular veins. The mass, configuration, and extent of the hepatic venous musculature ranges widely among species and is apparently capable of a corresponding range of constrictive action, from complete sphincteric throttling at innumerable points throughout the total drainage net to a modest reduction in capacity. Unfortunately, quantitative data are lacking and even the qualitative studies are so incomplete and fragmentary that it is impossible at present to assess the pattern and extent of change at different levels in a variety of species.

Spontaneous vasomotion appears to be randomly distributed, involved in strictly local shifts in volume but not in sweeping changes that move blood between

major units of the cardiovascular system. Studies based upon measurements of circulating splanchnic blood volume (regional dilution of I^{131} -labeled HSA) indicate that large changes in SBV may occur in the course of normal circulatory adjustments. In man, for example, both tilting into the upright position and exercise in recumbency have been found to induce splanchnic vasoconstriction with a fall in hepatic blood flow and splanchnic blood volume (42). It is not yet clear if a fall in distending pressure secondary to a more marked increase in the gastrointestinal and splenic inflow resistance than in hepatic venous outflow resistance, or if an active reduction in venous capacity is responsible. The fact that splanchnic denervation interferes with the response to tilting suggests that venoconstriction may be essential. Even if capacity is affected by venomotor activity, however, the extent of filling still depends upon the level of distending pressure and upon the manner in which distensibility is altered by "stretch" itself.

The arrangement of collagenous tissue in the adventitia, of muscle in the media, and of elastic tissue in the inner layers of vessels appears to result in an elastic behavior resembling that of three springs in parallel, the weakest representing the elastic tissue; the intermediate, muscle; and the stiffest, collagen. Interconnections and viscous changes in muscle and elastic tissue complicate the effort to devise a truly representative model (31, 241) [see also Chapters 24 and 26 of this volume]. The stretch or volume-pressure response curve yielded by isolated vessels proves to be concave to the pressure axis at low pressures, linear over an intermediate range, and finally convex at high pressures, suggesting that vascular distensibility is dominated initially by muscle, then, by elastic tissue and, finally, by collagen and fibrous tissue, as stretching occurs. Such a sigmoid curve has been obtained for canine splanchnic veins under a variety of conditions *in situ* (4, 7). The inflections occur at quite different pressures than they do in the aorta in conformity with the differences in structure. The concavity to the pressure axis and flattening occur at a much lower pressure (at about 40 cm saline as opposed to 140 mm Hg for the aorta) indicating dominance of fibrous tissue in the vein. A more marked increase in splanchnic venous distensibility is evident at physiologic pressures during the vasoconstrictive action of catecholamines, presumably because smooth muscle contributes more importantly under these circumstances. At lower pressures (below 15 cm saline), or when constriction results in a very low venous cross section, distensibility seems to de-

crease because of the operation of Laplace's law. After a period of time at high pressures the stretched vein does not return at once to the control volume when distending pressures are lowered to the control but assumes temporarily a new larger "zero volume." The viscous element which is responsible for this phenomenon is particularly difficult to explain. To some extent it may be referred to architectural adjustments such as slippage or uncoiling of intertwined elements, but all tissues in the wall, under sufficiently prolonged stress, are subject to a kind of viscous flow.

Alexander (4, 5, 7) has encountered the same problem in a somewhat different form in the course of a study of splanchnic venous distensibility in anesthetized dogs. Volumes of blood were injected by a motor-driven syringe at constant rates (10–250 ml./min) into the vein draining a loop of ileum isolated with all collateral vessels and nerves ligated and cut. Simultaneous arterial and venous pressure measurements permitted direct determination of pressure-volume relationships. By this means two types of distensibility were evident; 1) rapid elastic expansion yielding the expected sigmoid pressure-volume curve during the injection of relatively small volumes of blood and, 2) an additional, more slowly developing distention increasingly apparent at slower injection speeds. Alexander attributes the latter phenomenon to viscous creep and refers to it as "delayed compliance." Apparently, it is a continuously changing factor, possibly arising from the operation of multiple viscoelastic units arranged in series with the other components. Whatever the mechanism, delayed compliance may be of major importance in determining splanchnic vascular pooling at any distending portal venous pressure.

SECONDARY DETERMINANTS OF HEPATIC HEMODYNAMIC ADJUSTMENTS

Although the dimensions and the physical properties of all parts of the splanchnic vascular bed are primarily responsible for its over-all hemodynamic character, both circulatory stability and rearrangement are mediated by essential secondary mechanisms. Neural, humoral, and physical agents are demonstrably involved in the maintenance of the "reference" state and in the production of appropriate patterns of response. Change in any one of these factors elicits adjustments in all the others that must also be taken into account. A rich innervation assures integration and spread of vascular adjustments.

Whether neural activity is also responsible for the tone of vascular smooth muscle remains uncertain. No matter how defined, tone is not clearly dependent upon a continuous release of neural impulses. A very slow and undetectable discharge rate might be involved, but local factors, chemical and physical, still seem to take precedence over and replace neural regulation under certain circumstances. Neurohumoral transmitters, such as epinephrine, norepinephrine, and acetylcholine may also have considerable importance, contributing by local release in the maintenance of tone observed following denervation, for example, or by release into the circulation, in systemic integrations. Other local biochemical factors that must be considered to participate include oxygen, carbon dioxide, hydrogen ion, and metabolites like histamine or serotonin. Among the physical determinants are to be numbered intra-abdominal pressure, gravity, intestinal motility, and the changes associated with respiration and body movements.

Neural Determinants

The nerves of the liver, gall bladder, and bile ducts form a plexiform structure made up of numerous small ganglia with *a*) the anterior hepatic plexus (derived from the left portion of celiac plexus and the right abdominal branch of the left vagus) innervating the hepatic artery, and *b*) the posterior hepatic plexus (derived from the right portion of the celiac plexus and the branches of the right vagus that traverse the celiac plexus) investing the portal vein and bile duct (8, 190, 253). Ganglia required for parasympathetic synapses are not present. The spleen receives its supply almost entirely from the celiac plexus possibly with some contribution by the left phrenic nerve. Like the liver, the spleen receives no parasympathetic component (53, 294). Throughout the splanchnic bed bundles of nerves accompany blood vessels in their distribution to the tissues. Within the walls of the larger arteries subsidiary plexuses are arranged in a more or less orderly manner. An outer plexus in the adventitia, a deeper plexus between adventitia and media, and a plexus within the muscular media have been recognized. The complexity of these networks becomes progressively less marked in the vessel walls as caliber diminishes until at the capillary level it is difficult or impossible to find any evidence of specific innervation. The close association of vagal and sympathetic fibers in many regions does not imply an association in controlling vascular smooth muscle. Indeed the reverse seems to be true for vagal fibers

clearly innervate the smooth muscle of gastrointestinal tract, biliary tract, and pancreatic ducts (including secretory cells), but none has been traced to the blood vessels (8, 190, 249, 253). The innervation of the blood vessels within the splanchnic viscera appears to be derived exclusively from the sympathetic venous system. Moreover, all the sympathetic efferent pathways are now believed to be vasoconstrictive in activity.

Recent work (80) strongly supports the view that neither sympathetic nor dorsal root vasodilator fibers run to the splanchnic vasculature. The appearance of vasodilation evident in a rise in splanchnic blood flow with no blood pressure change, or in the face of a reduction in blood pressure, is therefore to be referred to "diminished vasoconstrictive tone." Although this conclusion is not universally acceptable, it must be admitted that a great weight of evidence gives it strong support. Direct stimulation of the splanchnic nerves, the hepatic plexus, or splenic nerve by a tetanizing current induces only a vasoconstrictive response *in vivo* or *in situ* which may be expressed by diminished blood flow, by a tendency for the liver and spleen to contract, by diminished cross section of intrahepatic vessels under direct observation, and by peripheral ischemia of the liver evident in micro-radiographic studies (11, 20, 25, 102, 104, 132, 161, 204, 270, 299). Variation in the extent of this response appears to be referable to differences in species studied and in the techniques employed, but the general agreement upon its qualitative features is unmistakable. In contrast, stimulation of the vagus produces little or no obvious change in intrahepatic or splanchnic resistance under similar circumstances (11, 104, 161, 270). Richins (248) has claimed that vasodilation may occur in the pancreas during stimulation of the celiac plexus after cutting the splanchnic nerves in the cat, because "quick-freezing" the pancreas during this period and careful preparation of microscopic sections of the tissue reveal larger cross sections of the arterioles and veins. This method is obviously open to question because it requires the assumption that fixation and preparation of the tissues for study do not affect the state of the vessels which obtains at the moment of freezing. Somewhat stronger support for active cholinergic hepatic vasodilation under special conditions has been put forward by Grayson and his associates (147, 157). These workers have attributed increments in hepatic blood flow, measured by internal calorimetry in intact unanesthetized rats and rabbits, during increments in arterial pressure produced by infusion of epinephrine or by transfusion of

rat blood, to reflex vasodilation because the response could be blocked by section of the right vagus, celiac neurectomy, atropine, and hexamethonium. They could not compute the changes in hepatic vascular resistance, however, and it seems more likely that the failure for blood flow to change after neural blockade during the rise in blood pressure is the result of active vasoconstriction. In this view, an intact innervation maintains flow by minimizing or blocking the fundamental vasoconstrictive response rather than by inducing vasodilation. In fact, Grayson and Ginsburg, like many other workers, have found that stimulation of the cut distal end of the vagus has no effect upon the hepatic circulation.

The undeniable fact of abdominal pain clearly indicates the presence of afferent pathways mediating visceral perception. Within and about the vessels of the splanchnic bed, myelinated and nonmyelinated fibers may be found ending freely in a fine meshwork or in Pacinian corpuscles. The first seem to accompany the vessels closely, branching dichotomously at each bifurcation and losing their myelin sheaths distal to the last branching. A filmy plexus of nonmyelinated nerves about the vessels extends into the avascular portions of the mesentery, onto the visceral peritoneum covering the intestines and bladder, and into the substance of the liver and kidney. Sheehan (271) found that small nerve ganglion cells appear in this network at wide intervals and concluded that single fibers "branch and anastomose in a true network arrangement." Fine twigs may be seen occasionally issuing from the plexus to end freely among the endothelial cells. Since they are demonstrable after removal of the splanchnic sympathetic chain and the vagi, they are presumably somatic in origin and possibly responsible for visceral sensations. Perhaps the most prominent and clearly definable afferent nerve endings associated with the splanchnic vasculature are the Pacinian corpuscles. These structures vary considerably in size and shape, ranging from easily visible ovoid bulbs (1.0 by 0.6 mm in diameter) to end bulbs measuring only 8 by 4 μ . Typically the Pacinian corpuscle is composed of a relatively thick, laminated capsule with a central core through which the main afferent nerve runs to its termination. It lies embedded in the vessel walls particularly in the pancreas, lymph nodes, and mesenteries or in the surrounding connective tissue and fat, usually arranged with the long axis parallel to the vessel. The number of corpuscles varies from species to species, widely distributed and common in the cat, but almost absent in the mesentery of the dog, rabbit, mouse,

and man (251). Electrophysiologic studies (139, 141) indicate that Pacinian corpuscles in the skin and mesenterics are sensitive to pressure changes. The spontaneous outflow of impulses in large afferent fibers in the splanchnic nerve seem to derive in the main from the Pacinian corpuscles. Gammon & Bronk (139), recording impulses from the peripheral end of the splanchnic nerve and its branches in cats, found group discharges synchronous with systolic arterial pressure peaks. During constant perfusion a sustained discharge was observed. Sarnoff & Yamada (259) have suggested that Pacinian corpuscles may mediate the changes in arterial pressure noted during manipulation of the splanchnic vessels, but recent work (40) indicates that extrasplanchnic baroreceptors are involved and that mesenteric pressure receptors do not contribute significantly, at least in species other than the cat. Nevertheless, afferent impulses originating in these areas may be implicated in local and central reflex arcs of importance to hepatic circulatory adjustments.

Impulses passing from the splanchnic bed by all these afferent routes evidently pass directly to the central venous system. Central representation of afferent fibers from the abdomen has been explored by a variety of methods. Bain *et al.* (18) found that stimulation of the central end of the divided splanchnic causes pupillary dilatation that is due to inhibition of the oculomotor nucleus and not to change in blood pressure, release of adrenaline, or activity of somatic afferent fibers, since it occurs after transection of the spinal cord between the fifth and sixth thoracic roots. Using this method as a means of detecting splanchnic afferent impulses they found that splanchnic afferents enter the cord from the sympathetic chain via the rami and the dorsal roots. No synaptic junctions seem to occur in the dorsal roots or in the lateral sympathetic ganglia which resemble those for sympathetic afferents in the sympathetic ganglia. According to Downman (113), stimulation of these fibers, in both cats and dogs, evokes detectable changes in cerebral action potentials within the trunk areas of somatic sensory representation, viz, contralateral area I and both contralateral and ipsilateral area II. The distribution and latency of the responses elicited by centripetal stimulation of the splanchnic nerve do not differ from those elicited by stimulation of a body-wall nerve. Amassian (9) reported similar cortical representation of visceral afferent impulses in the rabbit, monkey, dog, and cat with maximal primary cortical responses in the trunk region of contralateral areas I and II, with ipsilateral representation in area

II for the cat alone. The lack of correlation between the number of receptors and the intensity of responses suggests that splanchnic afferent projection may be but partially derived from Pacinian bodies. In addition, the projection to somatovisceral areas in the cortex raises additional doubt whether Pacinian corpuscles are primarily concerned in vascular readjustments rather than visceral sensation. The pathways through the cord have been mapped out to some extent by Aidar *et al.* (2) who found that action potentials were detectable in the cat to levels as high as the thalamus. Faster impulses course through the ipsilateral fasciculus and nucleus gracilis, internal arcuate fibers, and contralateral medial lemniscus to reach the thalamus. Slower impulses ascend in the lateral spinothalamic tracts. These findings have been confirmed by Gardner *et al.* (140) in studies of cortical projections of fast visceral afferent impulses in the cat and monkey. Since section of the dorsal funiculi does not always abolish cortical potentials evoked by stimulation of the splanchnic nerve they suggest that additional pathways are followed. The anatomical basis for reflex regulation of the hepatic and splanchnic circulation is clearly evident in these studies. The status of a controlling "vasomotor center" for the splanchnic bed is most obscure and it cannot be said with certainty that discrete splanchnic vasomotor representation is detectable within the cortex. Nevertheless, the cortical representation of visceral sensory and motor functions that may involve vascular smooth muscle seems to imply, on the one hand, a measure of influence upon splanchnic vascular changes by cortical activity directly, or, on the other, a reflection of visceral circulatory adjustments in cortical function.

Reflex responses almost certainly occur within the splanchnic and hepatic vasculature, although they are extremely difficult to characterize. Axon reflexes, involving afferent nerves like those responsible for the vasodilation of the "flare" in the skin during the "triple response," are not demonstrable (80). The phenomenon of "autoregulation" of hepatic blood flow is possibly an exception but, as noted above, a local stretch-and-response myogenic balance may be responsible (180). Expansion of the portal venous chamber may also elicit what Yamada & Burton (313) have referred to as a "veni-vasomotor reflex" characterized by arteriolar vasoconstriction proximal to the site of venous distention. Mesenteric arteriolar constriction observed during an elevation in portal venous pressure (268) may be explained on this basis but, here again, retrograde elevation of pressure to the level of the arterioles with the slowing of flow cannot

be eliminated as a cause for myogenic activation (180). The possibility that elevated hepatic venous pressure may induce reflex constriction in the hepatic arterioles and portal venules should be investigated. Similarly, conclusive demonstration of reflex changes mediated through spinal or corticohalamic centers via visceral afferent and efferent arcs is needed. There is little doubt that disturbance of splanchnic and hepatic vessels or stimulation of the central ends of the cut splanchnic nerves can give rise to marked changes in systemic hemodynamics. In both man and experimental animals traction on the mesenteric vessels is associated with a striking fall in arterial blood pressure provided the nerve supply is intact (230, 291), whereas splanchnic nerve stimulation results in transient arterial hypertension (141). The mechanisms of these reactions have not been subjected to detailed analysis and it is impossible at present to evaluate them in terms of venous return, peripheral vascular resistances, and local splanchnic and hepatic hemodynamics. The splanchnic vasculature also undergoes changes that appear to arise reflexly from other parts of the cardiovascular system, such as the carotid sinuses and great veins, but the usual difficulties in interpretation arise in connection with widespread and simultaneous circulatory adjustments in the remainder of the body. Perhaps the venoconstriction with increased carotid sinus tension and the venodilation during a fall in carotid sinus tension, or during distension of the inferior vena cava noted by Alexander (4, 5) in isolated innervated segments of the mesenteric veins, may be regarded as reasonably clear-cut evidence of reflex action, but even here uncertainty must remain regarding myogenic and humoral factors. Since the venodilator response is abolished by section of both vagi, these reservations seem ill-founded and a reflex with an afferent pathway via the vagal trunks may be postulated. Certainly afferent pathways from other parts of the body seem to be capable of activating visceral neural outflow and visceral vascular responses to peripheral stimulation. Heating or chilling the skin, a rise of pressure in the carotid sinus, distention of the inferior vena cava, and stimulation of the central end of the severed sciatic nerve have all been shown to elicit changes in the splanchnic vasculature (4, 5, 132). The blushing or blanching of the gastric or rectal mucosa during emotional responses (156, 192) also suggests that cortical activity, mediated by pathways that begin in the cortical motor projection of the splanchnic autonomic system, may affect the splanchnic and hepatic circulation.

Neurohumoral Determinants

Confusion regarding the neural determinants of flows and volumes within the splanchnic vessels is inevitable not only because responses are so complex but also because so little is known about the structure and function of the neurovascular units. Several types of nerve endings and receptors in vascular smooth muscle have been postulated to account for the varied responses to neural stimulation, to neurohumoral transmitters, and to blocking agents, but too little is known with assurance to permit the formulation of a fully satisfactory explanation. Recent work (161) suggests that norepinephrine alone is released from the nerve endings in the splanchnic vessels, and that receptors (β) responsive to circulatory epinephrine are present in the mesenteric, splenic, and hepatic vessels. Reserpine appears to be capable of releasing norepinephrine from splanchnic nerves, whereas the circulating amine, released by the adrenal medulla or introduced extraneously, can replenish the depleted store (69). Dopamine, the immediate precursor to norepinephrine, accounts for more than 95 per cent of the catecholamine demonstrable in the liver, jejunum, and colon where it appears to occur to a large extent in nonneural tissue (263). In the spleen and the pancreas, norepinephrine and epinephrine are found in approximately equal amounts as in adrenergic nerves. The large local supply of dopamine may imply that it has an action of its own. Acetylcholine has been found in large amounts in the spleens of some species (100) in accord with some evidence for cholinergic vasodilator receptors in the splenic vessels. The interplay of all these factors in any single neurovascular reaction is extremely difficult to follow, especially in view of differences in responsiveness, independent myogenic reactivity, and innervation within what Folkow (130) has referred to as the "series-coupled" and "parallel-coupled circuits" of the hepatic and splanchnic vasculature. Study of the pattern of response to individual chemical agents may ultimately clarify the mechanism of these responses and throw light upon the local and systemic role of the hormones themselves.

EPINEPHRINE AND NOREPINEPHRINE. To what extent the circulating catecholamines participate in vasomotor adjustments remains uncertain. Neural activity appears to exert a profound and selective action, effectively controlling splanchnic vasomotor function without need for an adjuvant (79, 130). The total range of control by direct sympathetic innervation is

also much more impressive than that of the adrenal medulla. Stimulation of the constrictor nerve fibers to the spleen, for example, causes marked contraction at rates as low as one impulse every other second, whereas large doses ($5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) of the medullary amines fail to cause more than 40 per cent contraction of the denervated spleen and an even smaller maximal response is produced by stimulation of the adrenal medullae. Celander (79) has concluded therefore that motor control of smooth muscle in blood vessels is dominated by the neural component. A corresponding predominance of the adrenal medullary hormones might apply to the sympathetic control of various metabolic processes. In emergency situations, moreover, it is possible that circulating hormones may have greater importance in determining vascular responses.

Both epinephrine and norepinephrine are clearly vasoconstrictor at all dosage levels in the perfused liver (12, 13, 25, 81, 132). In the early work adrenaline, known to be a mixture of *l*-epinephrine and *l*-norepinephrine, was used. Fortunately, the effect of epinephrine appears to dominate the vascular response to the mixture and the findings of the earlier studies do not differ substantially from those carried out more recently with *l*-epinephrine alone. The published data are often difficult to evaluate owing to the rapidity with which a succession of shifts occurs after introduction of the drugs. In part, the changes may be attributed to the rearrangements involved in passing from one state to another. Thus hepatic venous outflow may increase transiently as the liver shrinks with a reduction in intrahepatic blood volume, although inflow may fall and remain depressed. Differences in dosage are also obviously responsible for certain variants and may indeed give rise to irregularities in response pattern as the plasma concentration of the amine rises abruptly and then falls off following injection, reaching some parts of the vasculature early in high concentration, others later after dilution within the vessels. Finally, the physiologic state of the organ, whether liver, spleen, or intestine, is especially important. Congestion and increased resistance to perfusion arising from various causes, chiefly on deterioration with time, may greatly modify the response. With due allowance for all these considerations, however, both drugs appear to increase resistance to flow through the perfused hepatic (12, 13, 25, 81, 132), mesenteric (132, 269), and splenic (132) arterioles and to diminish the vascular capacity by venoconstriction and splenic contraction in all species. The facts are consistent with the presence of α -receptors mediated by norepinephrine (161).

The moderate vasodilation that may occur in the perfused mesenteric circuit, but not in the hepatic vessels, following the vasoconstrictive response to epinephrine may be regarded as evidence that β -receptors occur in the former and not in the latter, though the role of secondary changes with gut activity or of balanced shifts within the liver is not easily determined. Little information regarding the distribution of resistance and volume changes and the relative intensities of smooth muscle contraction between the different beds or even within the same one may be gleaned from these data.

In the intact animal, the responses are even more varied and complex, but the interplay of local circuits, pressures, and over-all cardiovascular adjustments may be made out more readily. The early work (132) on mammals yielded data generally consistent with the conclusion that epinephrine gives rise to an elevation in arterial and portal venous pressure in association with a reduction in splenic and hepatic volume, and diminished hepatic venous outflow. All these changes are in accord with those observed in the isolated systems and suggest, furthermore, that a more marked increase may develop in the hepatic vascular resistances than in mesenteric or splenic to account for the rise in portal venous pressure (1, 29, 47, 68, 104, 125, 142, 157, 159, 160, 163, 203, 210, 223, 281). Recent studies (1, 29, 47, 68, 125, 142, 157, 159, 160, 223, 281) indicate that norepinephrine may behave similarly. With greater detail and precision, however, interpretation has become somewhat more dubious. In the first place, it is now clear that epinephrine is essentially vasodilator in its total systemic effect, physiologic doses producing no change or even a fall in arterial mean pressure. Changes in flow must be equated with mean pressures and cannot be taken alone as evidence for vasodilation or vasoconstriction. Furthermore, much of the published material relates to the pattern of response observed after a single dose of the drug that induces a succession of conflicting local and reflex adjustments in which the assignment of cause and effect may be quite impossible. With constant infusion of epinephrine in unoperated, unanesthetized man (47), dog (142), and rat (157), hepatic venous outflow has been found to increase. Since the increment in flow exceeded or was out of phase with the increment in arterial mean pressure in the studies of man ($0.10 \mu\text{g}$ epinephrine $\text{kg}^{-1} \cdot \text{min}^{-1}$ for 30 min—BSP method) and dog ($0.25 \mu\text{g}$ $\text{kg}^{-1} \cdot \text{min}^{-1}$ for 1 min—blood flow velocity measured by implanted “thermistorsonde”) it may be concluded that over-all splanchnic vascular resistance decreased during these

experiments. In the rat, however, the rise in hepatic blood flow appeared to be less than the rise in arterial pressure indicating a local vasoconstriction less than that elsewhere in the body. Perhaps the differences in results are attributable to differences in the dosage—the lower doses inducing vasodilation of the mesenteric arterioles by stimulation of β -receptors. Certainly if portal venous pressure rises together with hepatic blood flow, as it seems to in man (187), it is possible that mesenteric vasodilation dominates the circulatory pattern, masking a moderate degree of intrahepatic vasoconstriction. Whether a reflex mediated through the central nervous system also contributes (21) remains uncertain. Norepinephrine, in contrast, is clearly vasoconstrictor but as with epinephrine, nothing is known about its effect upon the individual components in the intact hepatic and splanchnic bed. The data available are too fragmentary and unreliable to permit even a tentative synthesis.

Direct visual examination of the vessels within the splanchnic bed gives further support to the view that medullary amine usually tends to evoke a complex vasoconstrictive response. Seneviratne (270) and Wakim (299) agree in reporting that epinephrine applied directly to the surface of both the mammalian and amphibian liver produces contraction of the sinusoids, presumably as a result of constriction of hepatic arterioles and portal venules. No obvious effect upon the visible portal and hepatic veins was evident, however. A similar response was observed when the drug was injected into the portal vein. Interestingly, when the drug was given via the vena cava, the response was delayed and then replaced by "overactivity of the circulation in the whole liver, both as to number of active sinusoids and as to engorgement and rate of flow of blood in them." Similar responses have been reported in the gastrointestinal tract (132). Serial angiography also yields evidence of intrahepatic vasoconstriction in rat, rabbit, cat, dog, and the monkey (101). Intraportal injection of adrenalin (10–20 μg) resulted in changes like those produced by stimulation of the splanchnic nerves—i.e., a reduction in the number of fine vessels demonstrable by the circulating contrast medium together with an inconsistent diminution in calibre of the larger portal vessels. Daniel & Pritchard (101) noted further that "the rapid transhepatic passage of the portal flow which was observed after administration of adrenaline was associated in some but not all experiments with a change in the distribution of the contrast medium within the liver. . . . Frequently there was evidence

of an unequal distribution of the blood flow within the liver, illustrating that a differential use was being made by the portal venous blood of the various pathways through the liver." Much more work is required to sort out the data available and to evaluate by more precise methods the pattern of flow and pressure redistribution throughout the splanchnic bed during the action of epinephrine and norepinephrine.

ACETYLCHOLINE. Little consistent change appears in the isolated perfused splanchnic circulation following the administration of acetylcholine regardless of the method employed in its evaluation. Bauer *et al.* (25) were unable to obtain a definite response in the perfused liver of the dog, cat, or goat. If the "arterial tone" was "high" an intra-arterial injection of acetylcholine appeared to produce a relaxation comparable to that induced by histamine. Relatively small doses intra-arterially, however, acted upon the perfused goat's liver somewhat like adrenaline, that is, "arterial and portal tone were increased, liver volume diminished, and outflow practically unchanged. . . . this effect of acetylcholine was of the parasympathetic type, in that it was completely abolished by atropine, which left those of adrenaline and histamine unchanged." Chakravarti & Tripod (81) found that acetylcholine produced an easily detectable effect upon the circulation through the perfused liver if adrenaline were added to the perfusate in order to provide a "vasoconstricted state" in which a vasodilator action could be more easily elicited. Unlike adrenaline or histamine, acetylcholine had no action when injected into the portal vein. Andrews *et al.* (13) reported results similar to these. In most of their studies of the perfused canine liver, acetylcholine in doses ranging from 0.35 to 15.0 μg injected into the hepatic artery produced no change in arterial inflow, and a fall in both portal inflow and hepatic outflow with a rise in volume; but when adrenaline (0.1 μg per ml) was added to the perfusate acetylcholine raised the arterial inflow and slightly decreased portal venous inflow with a rise in both total outflow and volume. When injected into the portal vein, acetylcholine produced the same response as that produced by intra-arterial injection but 10 to 15 times the amount was required for an equivalent effect. Administration of eserine equalized the response to arterial and venous administration indicating that the difference might be due to greater destruction of acetylcholine in the portal vessels. They interpreted their results as indicating a weak vasoconstrictive response in the portal vein and hepatic

vein with little or no action upon the arterial circuit. Acetyl- β -methylcholine chloride and carbaminoyl chloride had a similar but longer action and did not produce different responses depending upon the route of administration, possibly because neither is readily destroyed by hepatic esterases. In subsequent studies of the effect of acetylcholine on the perfused hepatic vasculature of the monkey, cat, and rabbit, the same group (12) was impressed by the difficulty of obtaining reproducible responses for "the vascular responses showed considerable variation not only from species to species but also from time to time in the same animal." Similar equivocal results have been obtained in studies of isolated gut (27). Indeed, Bean & Sidky (27) have adduced evidence that the increase observed in blood flow through a perfused intestinal loop is attributable to the release of vasoactive materials locally rather than to a direct effect upon the vasculature. In the case of the spleen, acetylcholine does seem to have a direct effect at least insofar as strips of splenic muscle are concerned (53).

In his initial studies in 1918, Reid Hunt found that the liver of the intact dog shrank following intravenous administration of small doses but expanded with larger ones. A similar response was noted by McMichael (210) in the cat; the reduction in volume coincided with a fall in portal venous pressure and arterial pressure. In a similar study of the dog, Katz & Rodbard (182) also noted that acetylcholine caused an isolated fall in portal venous pressure that occurred at approximately the same time as a fall in arterial pressure and a rise in peripheral venous pressure. Portal venous flow (Ludwig stromuhr) tended to follow the portal venous pressure but did not fall to the same extent as arterial pressure, suggesting the development of mesenteric arteriolar dilatation. In more recent studies, the results also suggest that vasodilatation may occur in the liver though a change in flow has not been seen on direct observation (299). Using implanted devices to measure flow, Ginsburg & Grayson (147) and Gersmeyer & Gersmeyer (142) report an increase in hepatic venous outflow in rats and dogs during intravenous infusion of acetylcholine. Since arterial pressure fell at the same time, intra-hepatic resistance must have diminished. An increase in the volume of the gut and in mesenteric and gastric outflow has been noted by other workers (132, 219). The increment in hepatic blood flow cannot be explained entirely on this basis, however, since Ginsburg & Grayson (147) found that hepatic blood flow increased in the rat even when portal drainage was diverted from the liver. The spleen in the intact dog

apparently changes little in volume with a slight augmentation in arterial inflow despite arterial hypotension (164, 223).

Although the reactions, outlined above, to acetylcholine in the isolated and intact hepatic vasculature are obviously equivocal, a change of some kind does seem to occur. This fact is a little difficult to square with the absence of cholinergic innervation of the splanchnic and hepatic vessels and with the lack of any response to vagal neurectomy and stimulation. Cholinergic activity is definitely important in the function of the gastrointestinal musculature and of the glands of the biliary tract and pancreas. Hence, it is possible, as Bean & Sidky (27) have suggested, that secondary release of substances acting locally upon the blood vessels may be implicated. Brandon & Rand (53) and Burn & Rand (69) have recently brought forward a more attractive hypothesis that acetylcholine may release norepinephrine from stores in the tissues (in the nerves or chromaffin cells) which may be depleted by reserpine or neural degeneration and replaced by an infusion of norepinephrine. The variability of the results reported by many workers may well be explained, in part at least, by variation in the stores initially available and in the depletion of the neurotransmitter during the preparation of the tissues for study. Stimulation of the adrenal medulla and a general systemic response must also be taken into account in the interpretation of the effect of acetylcholine upon the hepatic circulation in the intact animal.

AUTONOMIC BLOCKADE. Autonomic denervation and chemical interference with autonomic activity have proved extremely helpful in the study of neurovascular function. As knowledge has accumulated, however, the complexities of the problem have become increasingly apparent. Surgical denervation is necessarily limited by the inaccessibility, diversity, and versatility of the nerve supply. A remarkable array of autonomic blocking agents is now available and growing in number and variety with each year. Unfortunately, the supply has outrun the laborious and gradual gathering of information regarding mode and site of action. Most of these substances interfere with both sympathetic and parasympathetic function, most produce confusing side effects unrelated to the splanchnic adrenergic blockade. Few have been studied with special attention to the effects upon hepatic inflow and outflow tracts. Since this is not the place to embark upon a detailed examination of the mechanisms of adrenergic and cholinergic blockade,

these matters will not be considered here. Interference with autonomic transmission, no matter how produced—whether by competition for receptor sites, by depletion of stored transmitters, by changes in membrane permeability or polarization, by change in synthesis or degradation, or even by surgery—makes possible a more meaningful appraisal of the relative importance of neural, humoral, and local circulatory determinants.

Denervation by any method does not seem to produce significant change in the blood flow in any part of the splanchnic and hepatic vascular bed. Mesenteric vasodilation, increased hepatic blood flow, and partial splenic contraction have been reported shortly after section of the splanchnic nerves, splenic nerve, and lumbodorsal sympathectomy, but these reactions seem to be temporary (132). Wilkins and his associates (310) have found that the EHBF was definitely higher and splanchnic vascular resistance “significantly” lower in 13 patients with hypertensive vascular disease 2 weeks after the Smithwick procedure. In six patients studied 4 to 6 months later, EHBF had returned to control values. Circulating splanchnic blood volume has also been found to increase after sympathectomy (42). High spinal anesthesia induces a fall in EHBF that may be accounted for by the coincidental fall in blood pressure in the absence of change in resting splanchnic resistance (201). Section of the vagus has no obvious effect (147).

Hexamethonium appears to be capable of blocking cholinergic transmission within autonomic ganglia though it does not block the response to sympathetic nerve stimulation (92, 133, 245). During ganglionic blockage, blood flow through the splanchnic bed decreased in dog and man only to the extent to which arterial pressure was reduced. The circulating splanchnic blood volume, in contrast, was found to expand significantly in the dog in the absence of detectable change in portal venous or sinusoidal pressures (92). These data are consistent with the view that basal arteriolar cross section in the splanchnic and hepatic beds at rest does not depend exclusively, if at all, upon the integrity of the autonomic nerve supply. Such a statement does not imply that no change occurred in the vascular smooth muscle. Whatever change in tone that may have occurred was evidently not sufficient to result in dilatation of the arterioles. It has been suggested that the contrasting arteriolar and venous reactions can be explained on the basis of Laplace's law, the difference in radii accounting chiefly for the relative effectiveness of the distending pressures at each level.

After administration of adrenergic blocking drugs (ergotamine, Dibenzyline, Dibenamine, Ilidar), epinephrine, norepinephrine, and neural stimulation fail to induce the usual arteriolar vasoconstriction in the liver, gastrointestinal tract, or spleen (159-161, 223). Norepinephrine appears to elicit little or no change of any kind under these circumstances, whereas epinephrine now causes vasodilation in the mesenteric and splenic vessels. The effect of neural stimulation is also reversed to some extent in the gut and spleen. Both are without any demonstrable effect upon the liver. These findings have been interpreted as evidence for vasodilator β -receptors in the mesenteric and splenic arterioles. Since study of the behavior of the veins, with special reference to their volume capacity, has not been made during adrenergic blockade, it is impossible to say whether these findings apply in general to the other vascular levels in each coupled system. It is also difficult to be certain whether dilation is an active or passive process or whether it involves the participation of other substances produced locally in response to epinephrine. There is no doubt that general blockade at any level is associated with a much more marked interference with vascular responses than is evident in the reversal of responses to epinephrine. Although the hemodynamic pattern at rest is not materially affected, any shift in position, imposition of stress, or environmental change unmasks a serious loss of capacity to make corrective adjustments. Tilting into the upright position, for example, results in a sharp drop in arterial pressure without eliciting the normal compensatory change in splanchnic vascular resistance. Pooling of blood within the splanchnic veins actually enhances the tendency to circulatory collapse (42). Neural and neurohumoral mechanisms may not be essential to maintenance of the resting state but they are clearly necessary for coordination in systemic responses.

Local Biochemical Determinants

Changes in blood flow result in corresponding changes in the delivery of oxygen and essential nutrients to, and in the removal of metabolites from, the tissues. Moreover, the associated activity of smooth muscle, the distention or deflation of capillaries, the alterations in interstitial pressure and in lymphatic drainage all impinge directly upon the cells. Metabolic processes are certainly affected by the secondary shifts in exchange and in the milieu intérieur and by the neurohumoral agents themselves concerned in these responses. In consequence, vasoactive materials

of various kinds, for the most part still uncharacterized, are released locally to play a more or less essential role in determining the pattern of circulatory adjustments. Since these materials rarely enter the blood in amounts sufficient for detection it is extremely difficult to evaluate their contribution. Tissue gas exchange is an exception because oxygen and carbon dioxide content of the blood entering and leaving the tissues is easily measured, but the influence of other agents must be studied indirectly.

OXYGEN. Even assessing the role of the blood gases is difficult because it cannot be said with any certainty how oxygen and carbon dioxide concentrations are distributed within the capillary network. The abundance of intercommunications makes it likely that a relatively uniform admixture of blood occurs. Nevertheless, the gradient between artery and vein must be reflected in a similar tissue differential so that vessels like those on the periphery of the hepatic lobules contain more highly oxygenated blood than those entering the central veins. Hypoxia, per se, seems to have relatively little effect upon the hepatic circulation. Hypoxia does result in the rapid deterioration of the perfused liver with the development of obvious swelling and decreased perfusibility, but whether these changes are to be ascribed to active vascular changes or to cellular swelling alone does not seem to have been subjected to systematic study (132). Torrance (291) found no evidence of any change in intrahepatic resistance to flow (internal calorimetry) in anesthetized rabbits after complete occlusion of the arterial and venous inflow tracts for 2 min. More prolonged (2 hours) ischemia of the liver in anesthetized, splenectomized dogs by occlusion of the hepatic artery and diversion of the portal inflow via an external shunt to the jugular vein produces a complex splanchnic vascular response, according to Selkurt (265, 266). He found that arterial blood flow dropped to 66 per cent of control on restoration of hepatic perfusion in association with a rise in intrahepatic and a fall in mesenteric resistances that together resulted in a marked increase in portal venous pressure. This work indicates, as does that of Torrance (291), that "reactive hyperemia" does not develop in the liver and it agrees with the more recent findings of Fischer *et al.* (128) in showing hepatic arteriolar constriction. Seneviratne (270) has noted sinusoidal dilatation after 1 hour of airway obstruction in mice and rats but in this instance carbon dioxide retention cannot be eliminated as the cause. Of course, prolonged hypoxia also elicits widespread compensatory adjustments

in the systemic circulation in which the hepatic and splanchnic bed might be expected to participate and which may produce changes opposed to those resulting from its action locally. Thus, perfusion of the mesenteric vasculature in an isolated innervated segment of a dog's intestine with hypoxic blood resulted in vasodilation and increased flow (26), in line with Selkurt's observations following protracted anoxia. When the animal was allowed to breathe a low oxygen mixture, however, reflex mesenteric vasoconstriction developed to a degree commensurate with the arterial oxygen content. Mesenteric and portal venous distensibility also decreases under these circumstances and it may be presumed that reflex venoconstriction contributes to the development of portal venous hypertension and results in a reduction in splanchnic blood volume during hypoxia.

CARBON DIOXIDE. The effect of hypercapnia is particularly difficult to follow owing to interference by an array of striking concomitant adjustments that include hyperventilation, peripheral vasodilation, hypertension, tachycardia, and an increase in cardiac output (247). To circumvent these obstacles, the splanchnic hemodynamic effects of elevated arterial carbon dioxide tensions were studied by Epstein and his associates (123) in normal human subjects during light general anesthesia with thiopental and nitrous oxide. Arterial carbon dioxide tension could be maintained at a constant level ($P_{aCO_2} = 56$ mm Hg on the average) by mechanically controlled respiration with an appropriate gas mixture following neuromuscular blockade with succinylcholine. Under these circumstances, interference with the response by an increase in ventilation could be eliminated. Nevertheless, the over-all response appeared to be inconsistent and erratic; mean arterial pressure rising in six subjects, falling in two, and not changing in five in association with a fall in EHBF in nine but with little or no change in EHBF in four. Splanchnic vascular resistance always increased, however, EHBF changing in accord with the balance between the perfusing pressure and resistance. Since blood flow tended to fall, the splanchnic vasoconstriction appeared usually to be somewhat in excess of that elsewhere in the body. Circulating splanchnic blood volume also decreased significantly in ten subjects and, since hypercapnia has been found to increase portal venous pressure, the change may be interpreted as evidence of constriction of splanchnic veins. The vasoconstrictive response is probably mediated through the central nervous system, since several investigators (132, 216) have found that in-

creased carbon dioxide tension in the blood perfusing splanchnic blood vessels including those of the liver, intestines, and spleen, elicits an arteriolar and venous constrictive response only if the splanchnic nerve supply is intact. After denervation, an elevation in PaCO_2 regularly induces vasodilation. Evidently this reflex pathway is relatively unaffected by cholinergic blockade and by light general anesthesia. Whether sufficiently high concentrations of carbon dioxide could overcome the opposing reflex activity and dilate the vessels directly remains unsettled, although Brickner *et al.* (66) have shown that mesenteric vasodilation may occur in the intact animal breathing gas mixtures that contain more than 8 per cent carbon dioxide. Splenic contraction induced by hypercapnia appears to involve activity of both splanchnic nerves and adrenals (235). Further work is required to elucidate the role of adrenergic mediators, the redistribution of blood within the splanchnic bed, and changes in the partition of hepatic inflow during hypercapnia. In addition, the effect of carbon dioxide released locally by metabolizing tissues, in amounts too small to affect the vasomotor centers, deserves investigation.

HISTAMINE. There is no doubt that carbon dioxide is added to the blood perfusing the tissues and that it is present, therefore, in varying concentrations which are certainly in excess of those in the arterial blood at the capillary level. Various other vasoactive materials also appear at approximately the same site, though relatively little is known regarding the mechanisms and character of their release. Electrolyte shifts and the production of hydrogen ion may be particularly important though very little is known about the part they play in the regulation of the microcirculation. Another vasoactive substance which appears in high concentration in all the tissues served by the splanchnic circulation is histamine (127). Although it has excited intense interest and extensive study for more than a half century, the function of histamine remains puzzling and controversial. Its action upon the hepatic and splanchnic circulations has received special attention. As early as 1899, it was discovered that a striking engorgement of the liver occurs in the dog during anaphylactic shock, and not long afterward the same phenomenon was observed following introduction of histamine into the portal vein (132). Since hepatic venous outflow decreased during engorgement of the liver, it was suggested that contraction of the venous musculature might act as a throttle mechanism to occlude the hepatic veins in the dog. Dale (25) and

others (12, 132) have confirmed these results, Dale showing that the response could be eliminated by slitting the hepatic veins of the perfused liver. Moreover, hepatic swelling proved to be less marked or absent altogether in animals like the cat, goat, or monkey that have thinly muscled hepatic veins. A diminution in portal inflow as well as in hepatic venous outflow also points to the development of increased resistance to perfusion. All these findings, together with the fact that histamine causes contraction of the spleen in most animals (132), point to vasoconstriction as the predominant effect. Elsewhere in the body, however, histamine causes striking arteriolar vasodilation, and in intact animals the net effect appears to be vasodilator also in the splanchnic bed. An increase in EHBF in the face of arterial hypotension has been observed in man after intramuscular injection of histamine phosphate (47). In unanesthetized dogs, moreover, Gersmeyer & Gersmeyer (142) have found that the velocity (thermistor) of portal venous blood flow increased sharply, although portal venous pressure rises very little as arterial and inferior vena caval pressures fall. Since it seems likely from what has been said above that outflow resistance is increased, the increments in portal pressure [which are quite marked in other studies (308)] and blood flow are most reasonably explained on the basis of mesenteric vasodilation in excess of augmented intrahepatic resistance. It is equally possible that hepatic arteriolar dilatation occurs. More precise and detailed information obtained under properly controlled conditions is needed to evaluate the simultaneous changes in splanchnic resistances and in venous capacity. The data at hand are in accord with growing evidence that "histamine may actively dilate arterioles at the same time that it actively constricts veins" (167) not only as a result of a direct action upon the vessels but also as a secondary result of adrenal medullary discharge (134, 228, 297). It is also possible that the action of many other substances is mediated through histamine release (228).

Still another substance released locally is serotonin, or 5-hydroxytryptamine, which has been identified and extensively studied in recent years. Selkurt (269) reports that it behaves like norepinephrine in causing vasoconstriction within the isolated mesenteric vessels of the dog but little is known about its effect upon the intrahepatic resistances or upon the volume of blood held within the total splanchnic bed, liver, or spleen. A steadily growing list of similar activating agents, including a miscellany of amines and peptides produced during tissue injury, is making manifest the

inadequacy of current concepts of cardiovascular regulation and stimulating numerous new investigations of the hepatic circulation.

Physical Determinants

Neural, neurohumoral, and local chemical influences operate for the most part reactively to alter vascular perfusion and content by changing arteriolar cross section and venous distensibility. As such they mediate adjustments but do not actually produce them. In contrast, external physical forces to which the abdominal viscera are exposed affect the hepatic and splanchnic vessels directly, frequently eliciting corrective or compensatory responses in which all the mechanisms discussed above are called into play. Movements and gaseous distention of the gastrointestinal tract compress, stretch, and variously deform the mesenteric vasculature with resultant change in flow and volume that must affect the delivery of blood to the liver by the portal vein. To what extent shifts within the mesenteric circuit, repartitioning of the total hepatic inflow, and redistribution of the splanchnic blood volume depend upon activity of the musculature of the gut remains uncertain. These problems are dealt with at length in Chapter 42 but must be touched upon here in order to indicate the potential importance of extravascular forces upon the hepatic blood supply. In this instance a reciprocal relationship obtains in that digestion, absorption, and the other functions of the gastrointestinal tract depend in turn upon the integrity of the mesenteric vasculature. Moreover, the integrated function of the liver and intestine hinges upon movement of absorbed material through the portal system to the liver. Exercise and respiration also impinge directly upon the hepatic circulation by raising intra-abdominal pressure and often by changing the position of the body. Both activities are associated with widespread cardiovascular changes affecting all parts of the body. The splanchnic vasculature participates in these reactions but it may actually be more markedly influenced directly by the associated physical effects.

INTRA-ABDOMINAL PRESSURE. The roughly cylindrical container holding the abdominal viscera and their vasculatures is almost completely muscular and capable of actively increasing the pressure within the peritoneal cavity. Moreover, the gastrointestinal system is periodically filled with fluids, solids, and gas, which occupy space and raise the pressure. As long as the pressures distending the vessels are in excess

of the circumambient pressures, there is little effect upon the resistance to flow or upon the forces conducive to blood flow. When the external pressure equals or exceeds the intraluminal pressure, by an amount determined by the elastic properties of the vessel, instability develops and collapse occurs at some critical pressure, provided the contents can be displaced. Any pressure increment is uniformly distributed throughout the abdomen, and blood, not being compressible, must move from an area of high pressure to one of low pressure to permit collapse of those vessels in which the intraluminal pressure is less than the external pressure. This occurs most readily at the diaphragm, across which the usual pressure drop is augmented. It may be inferred that with a rise in intra-abdominal pressure, blood in the veins close to the diaphragm is expressed and the vessels collapsed, thus producing a dam at the point of outlet. Since the arterial perfusing pressure is little affected, blood continues to pour into the system, but with the cessation of outflow, pressures gradually rise and inflow begins to diminish. When the local pressure at the point of collapse exceeds the critical opening pressure, outflow is restored and a new equilibrium established. Whether the expected increase in resistance so induced would tend to result in pooling of blood within the splanchnic circuit in the face of the forces operating to prevent distention must depend upon the relationship between the distribution of resistances and pressure gradients within the bed. Little information is available on which one may base further speculation. Increased intra-abdominal pressure has been found to reduce hepatic blood flow in man and experimental animals (47, 221), but precise localization of the sites of increased resistance and the character of volume capacity changes have not been satisfactorily settled.

GRAVITY. Gravitational force is also constantly operative in affecting intravascular pressures within the abdomen. Change of position results in a change in the hydrostatic pressure at every point in the vasculature by means of an addition or subtraction of a column of blood, the height of which depends upon the elastic properties of the vascular system. In computing the hydrostatic head at any point in the vessels, it is customary to take the center of the right atrium as the zero base line in recumbency. All pressures above that level in the supine position are negative with reference to it, and all below are positive. With a shift in position, the levels at which pressure in the arteries and veins remains unchanged may be taken

as the zero reference planes for the respective systems. In man, the arterial zero reference plane lies at the level of the diaphragm immediately after tilting into the upright position, with moderate change thereafter during vasomotor adjustments (309). Thus the elastic properties of the vasculature are such as to maintain the arterial pressure relatively constant at the level of the diaphragm; pressures at points above, falling, and below, rising, solely by the weight of the column of blood lying between each point and the zero reference level. The imposed blood column does not reach to the level of the uppermost body surface, e.g., the top of the head, because the closed elastic container exerts an attractive force in supporting that portion of the blood above the reference plane. A similar elastic buffering of hydrostatic shifts occurs in the veins. In both dog (86) and man (309) the venous side of the circulation is divided dynamically by cardiac activity into two separate hydrostatic compartments each with a separate zero reference plane. The immediate hydraulic changes with change of position are minimized on both the arterial and venous side and little immediate change in hemodynamics occurs in dog or man. Within a few seconds after assumption of the head-up position, however, the blood pressure does tend to fall and the heart rate to speed. Widespread vasoconstriction quickly checks the decline in arterial pressure. The splanchnic vasculature partakes in this general response, since it has been observed that splanchnic blood flow (EHBf) decreases significantly in man during orthostasis (99). This change is impaired in hypertensive patients following lumbodorsal sympathectomy (310). Circulating splanchnic blood volume is also reduced in the upright position presumably as a result of reflex alteration in the splanchnic vascular capacity (42). Further work is needed to define these changes in experimental animals.

RESPIRATION. The intra-abdominal pressure figures prominently in a more active sense as one of the forces involved in determining changes in splanchnic blood flow during respiration. Evaluation of the changes in pressure gradients and flows during the respiratory cycle is complicated by the difficulty of defining precisely what takes place in general terms. The number of factors involved and the variety of combinations possible under different circumstances makes generalization extremely hazardous. Even the dynamics of quiet breathing in recumbency in man can vary from time to time and from person to person, depending upon the individual pattern of abdominal

and thoracic muscular interplay, fatigue, extent of gastrointestinal and bladder filling, apprehension and the state of consciousness, muscular development, pulmonary or cardiac dysfunction, blood volume, and many other variables. It is to this irregularity that a remarkable diversity of opinion must be attributed (64, 132).

The fact that pressure within the thorax tends to be lower than atmospheric pressure during inspiration and somewhat higher during expiration is self-evident; the question that is difficult to answer is how and to what extent this phasic change in pressure is transmitted to the splanchnic vasculature. With descent of the diaphragm during inspiration the viscera are forced into the abdominal cavity, the vascular bed subjected to shortening and buckling, and the liver and spleen compressed to some extent as they are thrust out of the thorax. During expiration shifts in the opposite direction must occur. In association with these changes, opposing changes in intra-abdominal and thoracic pressure probably occur in such a way as to increase the pressure gradient between abdomen and thorax during inspiration and to reduce it during expiration. In the main, these inferences find support in the experimental record but they must be modified under many conditions. For example, it is possible for contraction of the abdominal muscles during expiration and relaxation during inspiration to counter the usual effect easily and to produce a reversed pattern. Indeed with maximal or laborious breathing in man, this seems to be the rule (73). In the upright position the superimposed hydrostatic pressure changes also have an effect. As noted above, the intra-abdominal pressure under these circumstances is governed to some extent—modified, of course, by muscular tone and activity—by the hydrostatic forces and the shift in arterial and venous zero reference planes. The weight of the upper abdominal viscera may be supported in part by the retractive forces of the thorax and its contents and, with impeded diaphragmatic excursion, an abdominal component in the respiratory pattern may figure more prominently. The magnitude and direction of thoraco-abdominal pressure shifts may have direct bearing upon blood flow into or out of the splanchnic vasculature or upon the quantity of blood held within it at any moment. This is so because collapse of the large draining venous channels may increase resistance to flow more than the rise in the pressure gradient tends to enhance it. This point has been much debated and still remains unsettled. On the one hand, Holt (174) and Duo-

marco & Rimini (117) believe that reduction in venous cross section at the level of the diaphragm and within the superior vena cava will impede return of blood to the heart during inspiration. Thus, radio-micrographic studies in the rat indicate that hepatic outflow may be more rapid during expiration (58). This thesis has been vigorously disputed, on the other hand, by the group with Wiggers in Cleveland which has included Opdyke (222), Alexander (3), and Brecher (64). These workers have shown that, though venous collapse may increase resistance with an increased pressure drop at the diaphragm, there is nonetheless an inspiratory increase in return, provided the tendency to venous collapse is not exaggerated by marked changes in the gradient, and provided alteration in the timing of phasic changes does not predispose to "depletion" of the venous chamber with resultant collapse. Both groups are probably correct, however, in view of the manner in which the response may be altered by extraneous factors, such as respiratory rate, position, and body size. During inspiration under ordinary circumstances the blood held in the hepatic venous tree and the inferior caval system flows out somewhat more rapidly than inflow so that venous return is initially augmented—and splanchnic outflow increased. The accompanying compression of outflow channels and the rise in intra-abdominal pressure would operate to reduce inflow so that net flow might change very little, rise or fall, depending upon the duration and frequency of the inspiration phase. Direct observation as well as measurement of flow bears out this conclusion, at least for the dog. The increased outflow resistance may actually conduce to portal venous pooling (3), again depending upon the interplay of all the other factors concerned. It may actually be rather difficult to define splanchnic flow and volume under these circumstances because the "depleting" phase of inspiration may be followed by filling during expiration not only from the arterial side but also by retrograde flow from the right atrium into the hepatic venous chamber as angiographic studies have shown. The effect of anatomic and dimensional differences requires further study.

EXERCISE. The effect of exercise must be determined to a large extent by the manner in which it affects respiratory activity, intra-abdominal pressure, and gas exchange as well as by release of various vaso-active agents. In quietly resting human subjects in recumbency, exercise (alternate leg raising) induces a significant reduction in both hepatic blood flow and

splanchnic blood volume presumably as a result of vasoconstrictive activity (298). Reallocation of splanchnic blood volume seems to occur quickly and may indeed play a role in the maintenance of cardiac output prior to the establishment of a new equilibrium. When blood pressure rises, the fall in splanchnic blood flow may not occur in spite of vasoconstriction. This phenomenon has been observed in dogs (superior mesenteric arterial flow measured by thermostromuhr) exercised on a treadmill (172). Possibly there was a similar absence of change in EHBF, in the face of an increment in hepatic temperature, in three normal human subjects studied by Graf (152). The Bromsulfalein clearance is of questionable value in evaluating the effect of exercise, since BSP extraction tends to increase in association with a rise in hepatic arteriovenous oxygen difference (34, 200). Barcroft and his associates (20) found that exercise (running) caused a significant splenic contraction in dogs and cats, which tended to persist in proportion to the duration and severity of exertion. A definite pattern of response of splanchnic arteriolar and venous constriction can be made out but, in view of the varied and opposing forces that are brought into play during exertion, a diversity of responses is probably the rule in normal life.

HEPATIC CIRCULATORY INTEGRATION AND DYSFUNCTION

Hepatosystemic Interrelationships

The participation of the hepatic and splanchnic circulation in general systemic reactions is usually difficult to detect and to delineate. The changes observed during exercise, assumption of the upright position, and respiration have been noted above because they entail a direct effect upon the intra-abdominal vasculature. In addition, any tendency for cardiac output or arterial pressure to fall or to rise is associated with concomitant changes in hepatic blood flow and splanchnic blood volume. In the main, these adjustments appear to provide for continued perfusion of the liver without undue interference with corrective responses elsewhere in the body to restore the status quo ante. Owing to the complexities of the splanchnic circuitry, however, the precise mechanisms of local adjustments are usually obscure. Little or no information is available regarding minor shifts. More is known about adjustments in such extreme disorders as circulatory collapse and congestive heart failure. Unfortunately, the need for

anesthesia in the experimental study of shock introduces an additional variable. General anesthesia with nitrous oxide, thiopental, or pentobarbital does not seem to affect EHBV and SBV provided gas exchange is carefully controlled (123, 124). Reactions may differ with the agent employed [splenic volume is increased, for example, by barbiturates and decreased by ether (132)] and more carefully controlled studies are necessary to evaluate the effects of different dosage levels and anesthetic planes. Anesthetic drugs also act like autonomic "blockers" to diminish responsiveness so that data collected in experimental studies may not be strictly relevant to the clinical state. Studies in man have been helpful for this reason, though complete control is impossible. The hepatic circulatory changes of congestive heart failure have been investigated only in man and, though the data are of great value, reliable evaluation must wait upon definitive studies of the condition produced experimentally in laboratory animals.

The effects of hemorrhage have been most extensively explored. In the anesthetized (pentobarbital) dog and rat, splanchnic blood flow and volume decrease during and following blood loss (136, 137, 179, 243, 267). Blood flow appears to diminish in proportion to the fall in arterial pressure. A transient vasoconstriction may occur but the general tendency appears to be rather in the direction of moderate vasodilation, particularly affecting the hepatic arterioles. Mesenteric arteriolar constriction may develop after prolonged hemorrhagic hypotension (96, 136) and may even be enhanced by the administration of norepinephrine, but there is no evidence that it is effective in sustaining arterial pressure (193). Portal venous pressure usually falls, too, presumably as a result of both the shift in the balance between input and output resistances (central venous pressure also falls) and the drop in arterial pressure. Splanchnic blood volume decreases more than the total blood volume (137, 243). The reduction in distending pressure is probably a major determinant of the shift, but venoconstriction, demonstrable in isolated preparations (6), must play a part also and undoubtedly accounts for the continued reduction in splanchnic blood volume following restoration of blood volume at a time when portal venous pressure tends to rise. Certainly, splenic contraction occurs in most species (132). The splanchnic venous reservoir evidently participates as a whole in homeostatic compensations by actively transferring blood into the central veins and sustaining the "circulating blood volume." This response continues to be detectable

even in the terminal irreversible phase (137, 243). How and to what extent anesthesia, adrenal medullary discharge and neural activity contribute to or modify hepatic vasomotor adjustments remains unsettled. Studies of changes during hemorrhage in human volunteers suggest that splanchnic vasoconstriction may be more prominent in the absence of anesthesia (28).

A definite vasoconstrictive pattern is clearly characteristic of congestive heart failure in patients with various cardiac diseases (236). In this situation, EHBV has been found to be reduced to the same extent as cardiac output despite maintenance or even elevation of the arterial blood pressure, indicating vasoconstriction no greater than that elsewhere in the body and certainly much less than that occurring in the kidney. A uniform contraction of hepatic and splanchnic arterioles probably occurs without much, if any, change in postsinusoidal or portal venular resistance, since wedged hepatic venous pressure did not differ from the free hepatic venous pressure by more than 2 mm Hg according to Rapaport and his associates (236). Circulating splanchnic blood volume is disproportionately increased by cardiac failure, at least in those patients in whom atrial and wedged hepatic venous pressure is elevated. There is no evidence at present of either splanchnic venoconstriction or venodilation and it is necessary to conclude, for the moment, that the distention is passive. The sequestration of a larger portion of the blood volume in the splanchnic bed may effectively reduce the load imposed upon the heart and, in so doing, serve as a compensatory device. The large volume of blood within the splanchnic veins is an ever-present hazard, however, for exertion, violent respiratory movements, or increased intra-abdominal pressure may displace a large volume of blood from the abdomen and throw an additional, and perhaps an overwhelming, burden upon the heart at almost any time. More data are needed to evaluate this possibility and to assess the role of the hepatic vasculature in the pathogenesis and therapy of congestive heart failure and other cardiovascular disorders.

Hepatosplanchnic Interrelationships

The interdependence of the liver and the gastrointestinal tract is self-evident. Digestion and absorption depend upon normal biliary secretion, while the enterohepatic circulation of bile salts and the release of secretin, in turn, determine bile flow and composition. Water, electrolytes, and various organic compounds

move rapidly from the gut into the portal venous blood and are carried directly to the liver. Since the bulk of the blood bathing the parenchymal cells comes from the portal vein, and since the sinusoidal walls are completely permeable to large molecules (209), the extracellular tissue fluid of the hepatic parenchyma must vary much more widely in composition, osmolarity, and acidity than interstitial fluid elsewhere in the body. Cellular function is undoubtedly influenced by the milieu intérieur as a whole as well as by certain active ingredients in it. The gastrointestinal tract may be said to control the chemical environment of liver cells not only by its absorptive activity but also by its oxygen consumption, for the liver must be content with the leavings of the gut. Owing to the difficulty of sampling portal venous blood, little is known about the fluctuations in the chemical composition of portal venous blood and their impact upon hepatocellular function. Much more, but still too little, is known about the manner in which portal venous pressures may be affected by the interplay between hepatic and splanchnic resistances.

The behavior of portal venous blood flow and pressure under normal conditions has been discussed at length above and the pattern of partition will be covered in another chapter. Since there is a lack of data on the distribution of flow and pressures throughout the total hepatosplanchnic vasculature, the relative importance of pre- and postportal vein resistances cannot be clearly defined. The fact that portal venous inflow usually accounts for some two-thirds to three-quarters of the hepatic venous outflow points to dominance by the preportal resistances (35, 37, 115, 132, 204, 255). The rise in portal venous pressure during the action of epinephrine may be ascribed therefore largely to mesenteric (subsuming under this term the total preportal bed) vasodilation, the fall with norepinephrine to mesenteric vasoconstriction. Vasopressin (103, 142, 308) has also been found to be a most effective agent in lowering portal venous pressure in man and dogs by contraction of the mesenteric arterioles in association with a reduction in hepatic blood flow. The resulting rearrangement of pressure gradients may result in a fall in sinusoidal pressure, so that the much weaker hepatic arteriolar constriction may be effectively countered by the rise in arteriosinusoidal pressure difference and hepatic arterial inflow actually increased (171). There is relatively little evidence of an actively maintained balance between arterial and portal

venous flow to the liver, although the arrangement of resistances noted above does lead to an apparent reciprocity when one or the other inflow is predominantly affected (36, 158). Ligation of the portal vein is thus immediately followed by an increase in hepatic arterial inflow, up to 100 per cent above control, and hepatic arterial ligation has a similar effect upon portal venous flow, but the increment fails to restore total flow to the control level (158, 254). Perhaps subsequent changes in tissue function set in train delayed corrective adjustments that assure adequate perfusion, but local mechanisms to provide immediately for reciprocity seem to be lacking. Indeed, portal venous pressure may be persistently reduced after hepatic arterial ligation so that an increment in portal inflow fails to make up the deficit in perfusion. A similar phenomenon has been encountered in patients with cirrhosis (52) where parenchymal cellular damage and extensive fibrosis have grossly deformed the architecture of the liver and its vasculature. The blood flow through the cirrhotic liver is significantly reduced by attenuation of the total vascular bed and by compression and distortion of the hepatic venous outflow tract. The resultant elevation in sinusoidal and portal venous pressure is often combined with a fall in plasma albumin concentration. Portal venous hypertension appears to be the primary event responsible for increased movement of fluid across capillary and sinusoidal walls and for the formation of ascites. Secondary circulatory, humoral, and renal changes are also essential features [see (16) and (196) for a recent examination of this problem]. The portal venous pressure may be markedly diminished by portacaval anastomosis, in association with a significant fall in hepatic blood flow that tends to persist without any evidence of hepatic arteriolar dilatation. Hepatic venous oxygen concentration is well below normal in cirrhotic patients and it falls still lower after establishment of a portacaval shunt, indicating further that hepatic arterial and portal venous inflows are not necessarily correlated. The relative independence of the two vascular supplies may indeed contribute in the pathogenesis and perpetuation of cirrhosis (289).

Under normal resting conditions the gastrointestinal vasculature could conceivably determine hepatic function through its domination of substrate supply, but, in fact, the hepatic blood supply appears to be adjusted to the metabolic requirements of the body as a whole. Digestion and absorption, as such, do not affect hepatic blood flow. Ingestion

of protein, possibly carbohydrates, but not fat, is followed by the development of hepatic hyperemia in man (54, 152, 200, 240). Reininger & Sapirstein (240) have found that hepatic blood flow increases in rats after a protein meal, in proportion to the rise in cardiac output and blood flow to other tissues that occurs at the same time. Similar changes in systemic and hepatic circulation have been detected in man during febrile reactions to pyrogenic agents (46, 152, 170) in association with increased total oxygen consumption. Liver temperature rises after protein feeding and during fever (152), presumably as a result of augmented hepatocellular metabolism. When hepatic oxygen consumption is increased by thyrotoxicosis, EHBF does not change appreciably (218). According to Bondy and others (38) uncontrolled human diabetes is not associated with a significant change in EHBF, although Lipscomb & Crandall (197) have observed high values in diabetic dogs. A definite increment in EHBF has been observed in dogs also during hyperglycemia produced by glucagon administration and hypoglycemia produced by insulin (112, 276, 279). Epinephrine release may be involved in the latter and must, indeed, be weighed in the evaluation of hepatic hyperemia, whatever its cause. Sympathoadrenal activation is an unlikely participant, however, in the action of *l*-hydrazinophthalazine which has been found (207) to elicit a pattern of circulatory and metabolic adjustments, in every respect like that produced by pyrogen, except that body temperature does not rise. If the expansion in splanchnic blood volume during the action of hydralazine in dogs is typical of the hepatic hyperemic reaction in general, it may be concluded that vascular smooth muscle is uniformly affected with simultaneous arteriolar and venous dilatation. Moreover, the tendency for arterial pressure to fall to low levels in these conditions may be the result of interference with venous return by "splanchnic pooling." Hyperemic responses deserve careful study not only for the light that may be cast upon normal hepatosplanchnic interrelationships but also for better understanding of derangements in integration that may be involved in the production of hepatic disorders.

Throughout the foregoing discussion attention has been directed chiefly to the local and systemic factors that may determine hepatic blood flow in health and disease. Admittedly the account is sketchy

owing to inadequacies of the author and the space available. An effort has been made to cover in some detail the elements of hepatic and splanchnic hemodynamics. The role of the preportal systems in the spleen, gastrointestinal tract, and pancreas have been alluded to frequently but it has been difficult to give these factors the weight they deserve, chiefly because the evidence available is so fragmentary and questionable. As noted at the outset, methodology must take first rank as a cause for uncertainty. Difficulty in generalization arises also from dependence upon data drawn from but one, or too few, experimental animal species; from acute responses trammelled by unphysiologic conditions of anesthesia, restraint, and surgery; and, finally, from portions, rather than the totality of any reaction. Emphasis has been placed upon correlation of structure and function. For this reason, among others, the arteriolar resistances have been stressed as determinants of flow and pressure gradients. The volume of blood contained within the vasculature has been assigned chiefly to the large veins and translocations or rearrangement of content ascribed, therefore, to alterations in venous smooth muscle function and inlet-outlet balance. Neither of these inferences is invalidated by the possibility touched upon at several points, that extravascular influences may dominate more slowly developing changes. Tissue turgor, fibrosis, extravascular cellular or fluid infiltration, and distortion by compression or traction may affect vascular path lengths and numbers, as well as cross sections, with a corresponding effect upon resistance and volume capacity. Much remains to be learned about the dynamics of flow in sinusoidal capillaries and it is possible that conventional explanations will ultimately prove inadequate. The hepatic vasculature and the splanchnic reservoir proximal to it participate in systemic circulatory reactions, but the evidence suggests that maintenance of hepatocellular function has priority and that homeostatic adjustments operate solely to produce a state that does not actively impair over-all compensation, without adding much to it. Perhaps the shift of blood from the splanchnic bed is helpful but the data cannot be construed to favor conclusively an active rather than a passive role. The liver is undoubtedly essential to metabolic activity, but the role of the hepatic circulation in metabolic homeostasis remains to be elucidated. In this direction, hepatic circulatory physiology may stand upon the threshold to significant discoveries.

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The flow of blood in the mesenteric vessels¹

EUGENE GRIM | *Department of Physiology, University of Minnesota, Minneapolis, Minnesota*

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THE MESENTERIC CIRCULATION is usually considered to be that part of the systemic circulation which supplies the stomach, small intestine, large intestine, pancreas, and spleen. These organs receive blood from all the branches of the celiac (except the hepatic proper), the superior mesenteric, and the inferior mesenteric arteries. They are not drained directly into the venous system as are most organs, but into the portal vein from which the blood passes through a second set of capillaries in the liver before entering the inferior vena cava.

Because of the peculiar anatomy of this venous drainage system, the flow of blood in the mesenteric vessels may be altered profoundly by factors which do not act directly on these vessels but rather change the resistance of the hepatic vasculature. This poses a problem for the investigator who uses the intact animal as the most "physiological" subject for study.

Great care must be exercised in the interpretation of the results of such studies, particularly when they disagree with those from investigations on the isolated mesenteric organs.

The mesenteric circulation as such has not previously been the subject of a comprehensive review, although it has been considered in a subsidiary fashion in reviews on the total splanchnic blood flow by such authors as La Croix (92) and Bradley (21). Even the standard textbooks of physiology, in which can be found sections devoted to the circulation through the heart, brain, lungs, kidneys, liver, and skeletal musculature, contain few statements concerning the circulation through the mesenteric organs.

In part, the cause of this is the relative scarcity of quantitative information on the subject and the many instances in which different investigators have published contradictory results. For the same reasons many of the statements that follow should be taken as tentative. This review might be better viewed as indicating guide lines for future research rather than as a definitive dissertation.

MAGNITUDE OF TOTAL MESENTERIC BLOOD FLOW

The total flow of blood through the mesenteric system can be most directly determined by measuring the flow through the portal vein. Since there has been no suitable method for this measurement in the human, all the available quantitative information has been obtained in experimental animals, especially the dog.

One of the earliest measurements of portal venous flow was made by Burton-Opitz (30) as a part of

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what probably remains to this day the most complete study of the flow of blood through the mesenteric organs. He placed a stromuhr in the portal veins of dogs anesthetized with ether and obtained a mean blood flow divided by the mean body weight of 14.3 kg of 19 ml per min per kg. His animals had relatively low arterial blood pressures, the average being about 100 mm Hg, and a normal mean portal vein pressure of 11 mm Hg.

In several subsequent studies made with thermostromuhrs, values between 16 and 20 ml per min per kg were obtained. These include Grab *et al.* (59), Soskin *et al.* (128), Grodins *et al.* (71), and Grindlay *et al.* (70). Some of the dogs used were unanesthetized; others were anesthetized with such agents as ether, chloralose, or sodium pentobarbital. Arterial blood pressure was given only in the report of Grab *et al.*, the mean being 100 mm Hg.

These investigations were performed with instruments which have since been severely criticized, the stromuhr because it introduces a flow resistance into the vessel in which it is placed and the thermostromuhr for a variety of reasons [see, for example, Gregg (68)].

MacLeod & Pearce (97) cannulated the thoracic vena cava of ether-anesthetized dogs, occluding it above and below the entrance of the hepatic veins with balloons, and collected the outflow before and after portal vein ligation. The mean total liver outflow in animals with an arterial blood pressure of about 140 mm Hg was 44 ml per min per kg. This was reduced by 60 per cent upon portal vein occlusion, indicating that the usual flow through the latter was about 26 ml per min per kg. Blalock & Mason (17) used a somewhat similar technique in unanesthetized dogs to measure the hepatic venous outflow immediately after hepatic arterial ligation and obtained a mean value of 24 ml per min per kg.

Electromagnetic flowmeters have been placed on the portal vein by several groups of investigators. Stewart *et al.* (129) and Drapanas *et al.* (41) found the mean portal flow to be 25 ml per min per kg at arterial pressures of about 140 mm Hg. Green *et al.* (66) obtained a lower value, 17 ml per min per kg, but the mean arterial pressure of their animals was only slightly above 100 mm Hg.

Direct measurements of portal venous flow by cannulation and collection of the blood was made by Heimburger *et al.* (75). They obtained a mean value of 30 ml per min per kg; however, since they collected the blood by gravity thus producing an

unphysiological, negative pressure in the portal vein, it seems likely that this value is too high.

The highest value for portal venous flow has been reported by Sapirstein (114). He injected radio-potassium and radorubidium into both rats and dogs and observed that the concentration of these isotopes in all organs except the brain remained nearly constant for a period of approximately 10 to 60 sec after injection. He concluded that the extraction ratios for these substances must necessarily be the same for all the organs, and hence that the fraction of injected isotope found in any organ was equal to the fraction of the cardiac output passing through the organ. By adding the isotope contents of the organs drained by the portal vein, Sapirstein found that 20 per cent of the cardiac output passed through them, a value which agrees well with the findings of the previous workers. However, when Sapirstein converted this value to units of flow per unit body weight, he obtained 34 ml per min per kg. The discrepancy arises from the fact that his dogs were small (6–8 kg) and had a mean cardiac output by the K⁴²-dilution technique of 170 ml per min per kg. In the larger animals used by most investigators (12–20 kg) the cardiac output is usually about 125 ml per min per kg, 20 per cent of which is 25 ml per min per kg.

The discrepancies among portal venous flows obtained by various workers would seem in large part to have been due to differences in arterial pressures rather than to the measurement procedures. The workers who found values of about 25 ml per min per kg studied dogs having arterial pressures of about 130 mm Hg, while those who observed 18 or 19 ml per min per kg used animals with pressures of about 100 mm Hg. It would appear that the portal venous blood flow in dogs of 10 to 20 kg body wt having a "normal" arterial pressure of 130 mm Hg is about 25 ml per min per kg. This is equivalent to about 20 per cent of the cardiac output or approximately 350 to 450 ml per min in a 15-kg animal. It does not seem that this value is too much affected by anesthesia with a variety of agents.

A very few measurements of total portal flow in other species can be found in the literature. Sapirstein and co-workers (109, 113, 133) in three separate studies found the portal flow in rats anesthetized with sodium pentobarbital to be 14, 16, and 20 per cent of the cardiac output. Fegler & Hill (44) using a thermodilution technique in sheep obtained a very high portal flow of 31 per cent of the cardiac output; however, as they pointed out, members of this

species are exceedingly sensitive to abdominal trauma. In the human, portal flow is usually estimated on the assumption (from studies with the dog) that two-thirds to three-fourths of the total hepatic flow as determined by the Bromsulfalein technique (800–850 ml/min m²) is derived from the portal vein. On this basis, the portal venous flow is 530 to 640 ml per min per m², somewhat less than 20 per cent of the cardiac output.

PARTITION OF TOTAL BLOOD FLOW

Major Organs

Two investigators, Burton-Opitz and Sapirstein, have measured the blood flow through all the major mesenteric organs. The former measured gastric flow (29) by placing a stromuhr in the gastrosplenic vein, ligating the pancreatic and splenic branches. Ligation of the gastroduodenal and pyloric veins presumably forced all the gastric venous drainage through anastomotic channels into the stromuhr. He obtained a mean flow of 0.25 ml per min per g of stomach in dogs with a mean arterial pressure of 85 mm Hg. In another group of animals (27) he placed the stromuhr in the common mesenteric vein thus obtaining the blood flow through all the intestine except the duodenum which is drained by the pancreaticoduodenal vein. At a mean arterial pressure of slightly less than 100 mm Hg, the mean flow was 0.31 ml per min per g of intestine. His measurements of pancreatic blood flow (31) were more difficult to make as this organ is supplied and drained by numerous vessels. He placed the stromuhr in the gastroduodenal artery, ligated the right gastroepiploic artery, and so obtained the flow through the superior pancreaticoduodenal artery. This vessel supplies the body of the pancreas and a portion of the duodenum. The head of the pancreas receives arterial blood by way of the inferior pancreaticoduodenal, a branch of the cranial (superior) mesenteric, and the tail of the organ by way of branches of the splenic artery. In two animals he was able to separate the body of the pancreas from the duodenum and so obtained the pancreatic flow alone. The mean flow was 0.8 ml per min per g at 110 mm Hg. To measure the splenic blood flow, Burton-Opitz placed the stromuhr in the splenic vein (28). In 10 animals, he obtained a mean flow of 0.58 ml per min per g at an arterial pressure of 98 mm Hg.

From Burton-Opitz' data, the weights of the

stomach, intestine, pancreas, and spleen in a 15-kg dog can be estimated as 250, 500, 50, and 70 g, respectively. The total blood flows through the same organs would be 60, 155, 40, and 40 ml per min, respectively, and the partition of the total mesenteric flow about 20, 55, 13, and 13 per cent. In Sapirstein's study (114) the partition of blood flow was determined directly. He obtained values of 13, 72, 8, and 7 per cent for the same organs.

The discrepancies in these two sets of data may be due to one or more of several factors. As stated earlier, Sapirstein's dogs were much smaller than those of Burton-Opitz. In the former the weight of the intestines was greater in relation to the weights of the other mesenteric organs than in the latter. Further, Sapirstein's dogs were anesthetized with sodium pentobarbital and presumably had arterial pressures 30 to 40 mm Hg higher. Finally, the measurement techniques used may have resulted in erroneous values for one or more organs in the study. It is possible that the resistance offered by the stromuhr to the intestinal venous outflow may have caused Burton-Opitz to underestimate the proportion of the total flow that passed through the gut. On the other hand, Sapirstein's method may result in either an underestimate or an overestimate of flow through an organ. His assumption that constancy of isotope content with time in all organs implies identical extraction ratios is not wholly justified. It is probably not too much in error as the extraction ratio for radiopotassium in the first few seconds after injection is nearly one for all organs. However, isotope constancy can be observed in the presence of different extraction ratios if the potassium ion concentrations of the organs differ, as they do.

In order to compare the data of Burton-Opitz and Sapirstein for any one organ with data obtained by other investigators, it is desirable to express the flows per unit weight of organ. Also, an attempt must be made to normalize the values to some kind of average animal. For Burton-Opitz' results this can be done by correcting to an arterial pressure of 130 to 140 mm Hg, assuming that the flow increases linearly with arterial-venous pressure difference. The following values are thus obtained: stomach, 0.4; intestine, 0.4; pancreas, 1.0; and spleen, 0.8 ml per min per g of tissue. Sapirstein's values for the same organs are 0.4, 0.7, 1.0, and 0.6, respectively. These values were obtained by taking the cardiac output to be 170 ml per min per kg. If Sapirstein's distribution is applied to 15- or 20-kg animals with a cardiac output of 125 ml per min per kg, his values

would all be reduced by some 25 per cent; that is, with the exception of the intestine, they would be lower than those of Burton-Opitz.

Of the other workers who have measured gastric blood flow, Boenheim (18) collected the venous drainage directly and obtained a mean flow of 0.26 ml per min per g at the very low arterial pressure of 60 mm Hg. Lim *et al.* (94) perfused with a donor dog an isolated surviving stomach and collected the venous outflow to find a mean value of 0.34 ml per min per g at a perfusion pressure of 100 mm Hg. Recently, Salmon *et al.* (112) used a method similar to that of Boenheim's in dogs with blood pressures of 130 to 150 mm Hg and obtained a mean flow of 0.37 ml per min per g.

The literature contains widely varying values for the blood flow through the intestines. Selkurt *et al.* (119) measured mesenteric venous outflow in dogs anesthetized with sodium pentobarbital and having pressures of 130 mm Hg or more. They found a mean flow of 8.7 ml per min per kg body wt which is equivalent to about 0.2 ml per min per g organ. In a later study with a rotameter, Selkurt (120) obtained flows 50 per cent or higher, but no body weights were given so direct comparison cannot be made.

A large number of measurements of venous outflow from segments of small intestine have been made in the writer's laboratory in the past few years. These were innervated and denervated segments, *in situ*, in dogs weighing 12 to 20 kg, anesthetized with sodium pentobarbital and having arterial pressures of 120 to 150 mm Hg. Although there was a large variation in values from segment to segment, the mean flows were about 0.6 ml per min per g, being slightly higher in the upper jejunum than in the lower ileum. These values were obtained with a venous pressure of zero. When the venous pressure was elevated to 10 mm Hg, the flow was generally reduced by 10 to 15 per cent.

Brodie and co-workers (23, 24) measured the blood flow through small intestinal segments plethysmographically and obtained a mean value of 0.4 ml per min per g. Neely & Turner (103) used a somewhat similar technique, measuring weight changes following venous occlusion to find 0.28 ml per min per g. Results of such studies as these two must be considered in light of the prompt rise in intestinal vascular resistance which follows an acute rise in venous pressure [see, for example, Selkurt & Johnson (122) and Johnson (85)].

Selkurt *et al.* (121) artificially perfused segments of

ileum and obtained flows with an arterial-venous pressure difference of 130 mm Hg of about 0.25 ml per min per g. This is much lower than flows obtained with similar preparations in this writer's laboratory. In our early work, very low flows were frequently obtained; however, more normal flows of 0.5 to 0.6 ml per min per g were usual in later experiments. The cause of the vasoconstriction in intestinal segments which follows arterial cannulation is not known to this writer, but it seems to be generally prevented by topical application of procaine at the site of the cannulation. This vasoconstriction can at times be so intense as to reduce blood flow to less than 0.05 ml per min per g.

Geber (54) has recently placed an electromagnetic flowmeter on cannulae placed in the arterial circuit of segments of dog's intestine and obtained very high flows. His values were duodenum, 1.38; jejunum, 0.98; ileum, 0.82; and colon, 0.73 ml per min per g. It is difficult to believe that these values are not falsely high. If correct, the intestinal venous outflow would be equal to or greater than the total portal venous flow as measured by most workers. It is possible that Geber trimmed the mesentery from the intestinal segments before weighing them. In some animals, this would reduce the segment weight by 25 to 50 per cent, and thus result in high estimates of the perfusion rates.

Several investigators have attempted to measure the blood flow through the cranial mesenteric artery of the dog. Trapold (132) using a Shipley rotameter and Deal & Green (38) using an electromagnetic flowmeter found flows in the range of 10 to 60 ml per min, the average being less than 2 ml per min per kg body wt. This is a surprisingly low value; with the exception of the flow through the relatively small caudal mesenteric artery, the cranial artery supplies the same tissues as are drained by the common mesenteric vein. It is possible that manipulation of the mesenteric artery may result in vasoconstriction just as does cannulation of the intestinal arteries. Cull *et al.* (36) obtained higher flows in the cranial mesenteric artery (120 ml min in dogs of unspecified weights), but these are still significantly lower than would be expected. Grodins *et al.* (71) used a thermomicroprobe to obtain mesenteric artery flows of a more expected value of 12 ml per min per kg. Meyer (100) ligated the gastroduodenal and caudal mesenteric arteries and collected venous outflow from that part of the gut supplied by the cranial artery (jejunum, ileum, and proximal portion of the colon). He obtained flows of the same order as those of

Grodins, 180 to 190 ml per min from tissue averaging 370 g in weight (0.5 ml min g).

The studies on pancreatic blood flow have not generally supplied sufficient information to permit calculation of the flows per unit organ weight; hence comparison with the values of Burton-Opitz and Sapirstein are difficult. Babkin & Starling (6) perfused the superior pancreaticoduodenal artery from a heart-lung preparation and collected the venous outflow in dogs under morphine and chloralose anesthesia. They did not separate the pancreas from the duodenum. In one experiment they observed a control flow of 100 ml per min and in another 30 to 40 ml per min. No animal or organ weights were given. Gayet & Guillaume (52, 53) measured the outflow from the superior pancreatic vein in dogs and obtained resting values of 20 to 25 ml per min in animals of unspecified weight. Bennett & Still (14) placed a stromuhr in the superior pancreaticoduodenal vein of dogs of 8 to 9-kg body wt. Various anesthetic agents were used: sodium barbital, sodium amytal, and chloralose. They separated the pancreas from the duodenum and estimated that they were measuring the drainage of about one-half of the organ. The mean flow was 6.2 ml per min. This is of the order of 0.5 to 0.6 ml per min per g of tissue.

Grindley *et al.* (69) used a thermostromuhr to measure splenic blood flow in unanesthetized dogs. They obtained a mean value of 95 ml per min which is 50 per cent higher than that observed by Burton-Opitz. Otis *et al.* (104) employed electromagnetic flowmeters in dogs anesthetized with sodium pentobarbital and observed flows of about 30 ml per min in dogs of approximately the same weight. While this is much lower than observed by Burton-Opitz, it is in better agreement with the findings of Sapirstein. It is important to note that in expressing splenic blood flows per unit weight of organ, care must be exercised in the definition of the organ weight. Burton-Opitz found the spleen of his etherized dogs to weigh about 5 g per kg body wt. postmortem. As is well known, the spleen in animals anesthetized with pentobarbital weigh three to four times this, and Burton-Opitz' value of 0.8 ml per min per g would accordingly be reduced to 0.2 or 0.25 ml per min per g.

An attempt has been made to summarize all this data and to choose mean values which it is hoped approximate the situation in the intact dog; these are shown in table 1.

TABLE 1. *Blood Flow Through Mesenteric Organs of a 15-kg Dog Having an Arterial Blood Pressure of Approximately 130 mm Hg*

| Organ | Weight, g | Blood Flow | | |
|-----------|------------|-----------------|---------------|------------|
| | | ml min, g organ | ml/min animal | % of total |
| Stomach | 250 | 0.35 | 90 | 20 |
| Intestine | 500 | 0.5 | 250 | 60 |
| Pancreas | 50 | 0.8 | 40 | 10 |
| Spleen | 70* (250†) | 0.7* (0.2†) | 50 | 10 |

* Weight and flow in ether anesthesia. † Same in pentobarbital anesthesia.

Individual Tissues

Since the arterial supply and venous drainage of any tissue of a complex organ is by way of thousands of microscopic vessels, the usual direct methods cannot be employed to measure tissue blood flow. Instead, one must resort to methods based on the Fick principle.

Shore *et al.* (125), in a study of the secretion of basic drugs by canine gastric mucosa, found that the clearance rates of drugs having a pK of 5 or greater were equal and maximal for all the drugs tested. They concluded that this maximal value was equal to the mucosal blood flow. By measurement of the concentration of drug in the gastropyloric venous blood, they further discovered that the maximal clearance was about two-thirds of the total gastric blood flow; that is, approximately two-thirds of the total flow passed through the secreting portion of the mucosa. Schanker *et al.* (116) determined the clearance of one of the same drugs, aniline, by the rat stomach to be 75 ml per hour. On the basis of Sapirstein's findings, the total gastric blood flow in rats of the same size is 140 to 150 ml per hour. Thus, a minimum of one-half the total flow passes through the secreting mucosa.

Two different techniques have been employed by workers in this writer's laboratory to obtain a reasonably complete analysis of the distribution of blood flow through the tissues of the canine small intestine. Lindseth (95) employed glass microspheres of 12 μ in diameter labeled with Na²⁴ in dogs anesthetized with sodium pentobarbital. After the injection of a small quantity of the spheres into an intestinal artery, the segment supplied by that artery was removed and separated into its component tissues: mucosa, submucosa, muscularis, and mesentery. The fraction of the injected spheres in each tissue was de-

terminated by counting the isotope. Since the spheres were too small to lodge in any arteriovenous vessels except the capillaries, this fraction should represent the proportion of the total blood flow which passed through the capillaries of that tissue. For fasted ileal segments the proportions were mucosa, 38 per cent; submucosa, 8 per cent; muscularis, 22 per cent; and mesentery, 15 per cent. The remaining 17 per cent passed through vessels larger than $12\ \mu$ in diameter. The flows in milliliters per minute per gram of tissue were mucosa, 0.42; submucosa, 0.34; muscularis, 0.48; and mesentery, 0.69. For fasted jejunal segments, the distribution and flows per gram of tissue were not significantly different, except that the total blood flow was somewhat higher, the difference passing through arteriovenous channels larger than $12\ \mu$.

The other method was employed by Rayner *et al.* (107) in dogs under morphine analgesia and by Weiner (137) in dogs under pentobarbital anesthesia. Segments of fasted ileum were artificially perfused with blood containing deuterium oxide for short periods of time. On the assumption that the kinetics of distribution of isotopic water is blood-flow limited, the perfusion rate for each tissue was calculated from its isotopic content at the end of the perfusion period. In milliliters per minute per gram of tissue, Rayner *et al.* obtained the following flows: mucosa, 0.38; submucosa, 0.56; muscularis, 0.66; and mesentery, 0.23. Weiner found 0.42, 0.50, 0.51, and 0.16 for the same tissues.

Comparison of the results obtained with the microsphere and with the D_2O methods in pentobarbital-anesthetized animals shows the major discrepancy to be in the estimation of flow through the mesentery. It seems most likely that the D_2O technique underestimates flow through this fatty tissue. The higher submucosal flow obtained with the latter technique may indicate that some D_2O exchange occurs across the walls of arteriovenous bridges which abound in that tissue.

Vessels of Different Sizes

Many histological studies have demonstrated that the arterioles and venules of the mesenteric organs are connected by vessels varying from true capillaries with a diameter of $10\ \mu$ or less to arteriovenous bridges or throughfares with diameters in the range 10 to $20\ \mu$ to true arteriovenous anastomoses having diameters in excess of $20\ \mu$. The distribution of organ blood flow to these different-sized channels has been investigated in only a very few instances.

Walder (135) estimated the flow through arteriovenous anastomoses in the artificially perfused human stomach by measuring the perfusion rate before and after presumably blocking all the capillaries with starch granules. On this basis, he concluded that the proportion of the total flow passing through arteriovenous anastomoses was about 5 per cent.

Lindseth (95) measured the blood flow through arteriovenous vessels of different sizes by injecting small, known numbers of radioactive spheres of different diameters into the arterial supply of the canine intestine. He employed spheres with mean diameters of 12 , 20 , and $44\ \mu$. Measurement of the number of such spheres which passed through the organ into the venous blood permitted him to calculate the partition of the total blood flow among the arteriovenous channels of the three sizes. He found that essentially no $44\ \mu$ spheres passed through in either the jejunum or ileum; 3 to 4 per cent of the blood flowed through vessels having diameters between 20 and $44\ \mu$; and 24 per cent in the jejunum and 14 per cent in the ileum passed through vessels 12 to $20\ \mu$ in diameter. Thus, in the fasting canine intestine, the fraction of the total blood flow which passes through true arteriovenous anastomoses (vessels greater than $20\ \mu$ in diameter) is very small. However, a quite significant fraction may flow through arteriovenous bridges and hence bypass the capillaries.

The finding that such a small fraction of the blood passes through channels larger than $20\ \mu$ is in agreement with results of investigations by Gordon *et al.* (58). These workers estimated the size of the largest arteriovenous channels in the intestine of rats and rabbits anesthetized with sodium pentobarbital by determining the minimum pressure required to force mercury, air, or kerosene through the vasculature of these organs. They concluded that the intestines contain no vessels larger than $25\ \mu$ in diameter.

Several investigators have injected large quantities of glass microspheres into the arteries supplying one of the mesenteric organs and determined the maximum size of the spheres which passed through. Sherman & Newman (124) did this in the stomach and duodenum of the dog and recovered some spheres as large as 100 to $180\ \mu$. Prinzmetal (106) reported spheres of 160 to $370\ \mu$ in the splenic vein of dogs studied in the same way. Walder (134) made a more complete study and used much smaller quantities of spheres in the artificially perfused human stomach. He found the diameter of the largest spheres to pass through were $140\ \mu$ and of the mean

100 μ . The fraction of injected spheres which passed through was not determined in these investigations.

MESENTERIC BLOOD VOLUME

Attempts to measure the volume of blood in the mesenteric organs of the dog are complicated by the presence of the spleen, the quantity of blood in this organ varying greatly with the nature of the anesthetic agent. Further, since its hematocrit is much higher than that of the body as a whole, estimates of mesenteric blood volume from the distribution of labeled red cells can be expected to be too high and those made with labeled plasma constituents too low. A correct value can be obtained only if both red cell and plasma volume are measured simultaneously.

Although such a direct study has not been made, it is possible to approximate the mesenteric blood volume by combining the results of several different investigations. One of the most pertinent of these is Johnstone's (87). He placed ligatures around the esophageal-gastric junction and the rectum of dogs anesthetized with sodium pentobarbital, and injected P^{32} -labeled red cells. After a 5-min mixing period, he clamped the celiac axis, mesenteric arteries, and portal vein, simultaneously. By analyzing these organs for P^{32} , he found that they contained 22 per cent of the injected red cells.

To calculate the blood volume from this observation, the hematocrit of the mesenteric organs, especially the spleen, must be known. Allen & Reeve (2) determined both the red cell and plasma volume of spleens from pentobarbital-anesthetized dogs. They found the blood volume to be 4 to 10 per cent of the total body blood volume and the hematocrit 1.7 times that of the large vessels. The ratio of the large vessel hematocrit to that of the whole body is a variable quantity as pointed out by Baker & Remington (7); however, in dogs anesthetized with pentobarbital like those of Allen and Reeve, Reeve *et al.* (108) found the ratio to be about 0.9; that is, the splenic hematocrit would be about 50 per cent greater than that of the whole body. The dogs of Allen and Reeve were only lightly anesthetized and other studies have shown that the spleen in more deeply anesthetized animals may contain more than 10 per cent of the total blood volume. A reasonable estimate, though, would be that the spleens of dogs anesthetized with pentobarbital have 10 per cent of the total blood volume and 15 per cent of the total red cell mass. Combining this with Johnstone's

observations, the other mesenteric organs would contain 7 per cent of the body's red cells and, assuming their hematocrit to be about the same as the body's, 7 per cent of the total blood volume. Thus, the mesenteric organs would hold 17 per cent of the total blood volume, or about 15 ml per kg body wt in dogs under pentobarbital anesthesia. Under ether anesthesia, with the spleen essentially empty of blood, this value would drop to nearly 7 per cent (6 ml/kg). In unanesthetized animals, the volume should be between these two extremes. Friedman (49) has shown that the spleens of unanesthetized mice contains about one-half as much blood as those of animals under pentobarbital anesthesia.

Horvath *et al.* (82) used the "exclusion technique" of Delorme and co-workers (39) to determine the volume of blood in the mesenteric organs plus the liver. They found this to be 21 per cent of the total blood volume, 6 per cent in the hepatic, 6 per cent in the splenic, and 9 per cent in the mesenteric artery beds. Most of their experiments were with I^{131} -labeled albumin and hence probably gave underestimates of the blood volume, particularly of the splenic artery distribution. Their findings do not, therefore, disagree significantly with the estimate given above.

Measurement of the volume of blood contained in the minute vessels of some of the mesenteric organs was made by Gibson *et al.* (55) in dogs under light morphine narcosis. These workers determined both the red cell and plasma content of the drained organs and found the stomach and intestine to contain 0.04 ml blood per g tissue and the spleen 0.5 ml per g. The blood volume of organs of the rat was determined by Everett *et al.* (43) with Fe^{59} -labeled cells and I^{131} -labeled plasma in quick-frozen animals. For the small intestine they obtained a blood content of 0.034 ml per g and for the spleen, 0.17 ml per g. Rieke & Everett (111) made similar measurements with rats under pentobarbital anesthesia and found 0.047 ml per g of intestine and 0.32 ml per g of spleen.

If the minute vessels of the stomach and intestine contain about 0.04 ml per g of blood, these organs in a 15-kg dog would contain about 30 ml of blood, $\frac{2}{3}$ in the intestine. Thus, a dog not too deeply anesthetized with pentobarbital would have a total mesenteric blood volume of some 200 to 250 ml, 60 per cent of which would be in the spleen, 10 to 15 per cent in the minute vessels of the other organs, and the remaining 25 to 30 per cent in the large gastric and intestinal vessels. This partition as well as the

total volume can, of course, vary greatly in both physiological and pathological states.

FACTORS AFFECTING THE BLOOD FLOW AND ITS DISTRIBUTION

Stomach

Stimulation of the splanchnic nerves decreases the blood flow through the gastric vessels. This has been demonstrated by Burton-Opitz (29) in the ether-anesthetized dog, by Lim *et al.* (94) in the blood-perfused canine stomach, by Thompson & Vane (131) in cats anesthetized with chloralose, and by Walder (134) in Ringer-perfused human stomachs. Friesen & Hemingway (51), using a calorimetric method, showed that the mucosal flow decreased during sympathetic stimulation in unanesthetized dogs. In the rat, Schnitzlein (117) observed blanching of the gastric mucosa during splanchnic stimulation and Arabehty *et al.* (5) found engorgement following block or section of the same nerves. The latter observations, it should be emphasized, are of the mucosal blood volume and do not necessarily demonstrate that the blood flow through this tissue is decreased by sympathetic stimulation.

Care should be exercised in the interpretation of the many observations of changes in mucosal color, labeled red cell content, India ink density, etc. produced by nervous stimulation or drug administration. Blanching may well occur without significant change in the blood flow or even in face of an increased blood flow. Engorgement may accompany an increase in flow resistance, especially if that occurs as a consequence of venular constriction. Such observations can properly be taken as indicating changes in blood volume only.

Many of the investigations cited above (18, 94, 131, 134) have shown that the influence of epinephrine on the gastric circulation is quite similar to that of splanchnic stimulation. In addition, Henning *et al.* (76) using an acetylene clearance method observed an apparent reduction in human mucosal blood flow in response to administration of sympathomimetic drugs. Peters & Womack (105) found that epinephrine produced mucosal blanching in the dog. They also injected glass microspheres into the arterial supply and, finding more large spheres in the venous outflow than in control studies, concluded that adrenaline dilated arteriovenous anastomoses. This latter is not in agreement with the findings of Walder (135),

who concluded that the increase in arteriovenous anastomotic flow was due only to increased resistance in the capillary system rather than anastomotic dilation. Miller & Haszczyc (101) found that epinephrine reduced the number of blood-filled capillaries in biopsy specimens from human gastrotomies. Dolcini *et al.* (40) made similar observations in the rat. Schnitzlein (117) observed mucosal engorgement in rats given ergotoxine to block adrenergic influences, although the same drug in Walder's (134) experiments did not alter the perfusion rate significantly from control values.

Burton-Opitz (29), Lim *et al.* (94), Boenheim (18), Friesen & Hemingway (51) all found little or no effect of vagal stimulation on gastric blood flow unless peristaltic activity appeared, in which case blood flow declined. Schnitzlein (117) did observe mucosal engorgement in the rat with vagal stimulation. He also found that the application of acetylcholine to the gastric muscularis produced contractions and mucosal blanching. Necheles *et al.* (102) found that acetylcholine usually produced vasoconstriction in Ringer-perfused rat stomachs. It was stated that this was not the consequence of increased motor activity, although the latter was not recorded. Walder (134) reported that acetylcholine in some cases reduced and in others increased the rate of perfusion through human stomachs. He made no comments concerning motor activity.

In the studies already referred to by Lim *et al.*, Thompson and Vane, and Walder, histamine caused a vasodilation in the stomach. Cutting *et al.* (37) also observed increased gastric blood flow in cats with this compound. Richards *et al.* (110), using a calorimetric method, found that histamine increased mucosal flow in the human stomach. In contradistinction, Necheles *et al.* (102) could observe no effect of histamine in their Ringer-perfused rat stomachs; and Boenheim (18) reported a decrease in etherized dogs, although the arterial pressures of his animals were very low. Peters & Womack (105) observed a marked increase in the mucosal content of arterially injected starch granules and India ink during histamine administration in the dog. Miller & Haszczyc (101) also saw an increase in filled capillaries in human mucosa as a consequence of the drug. Kimbel *et al.* (90), on the other hand, found a marked decrease in the P^{32} -labeled red cell content of the gastric mucosa of polycythemic patients given histamine.

The influence of several other chemicals on gastric blood flow has also been studied. Cutting *et al.* (37)

found that pilocarpine increased flow in the cat. Bishton (16) made a similar observation in guinea pigs when the pilocarpine was administered topically. Schnitzlein (117) saw mucosal engorgement in the rat under the influence of this drug. Lim *et al.* (94) observed little effect of Pitressin in their perfused preparation, but both Cutting *et al.* and Boenheim (18) found a decrease in flow under the influence of this hormonal preparation. Lim *et al.* found that sodium nitrite and Cutting's group that erythrol tetranitrate increased flow. Dolcini and co-workers (40) observed an increase in the gastric mucosal content of arterially administered India ink in the rat given serotonin or 5-hydroxytryptophan.

Salmon *et al.* (112) demonstrated that cooling the dog stomach to 15 C reduced the blood flow to 30 to 40 per cent of control. Heating was shown by Cutting's group to have the opposite effect.

Richards *et al.* (110) found that a variety of emotional states, anxiety, tension, resentment, all increased flow in the human gastric mucosa as evidenced by the increase of heat uptake by the luminal surface. Wolf & Wolff (138) made an extensive study of color changes (i.e., blood volume changes) in a human gastrectomy. There was an increase in redness following administration of histamine, alcohol, beef juice, acetylcholine, exposure to local warming, during discussion of food and coincident with evidence of hostility. Blanching occurred during fear, sadness, discouragement, exposure to cold, and after administration of epinephrine, ergotamine, or Pitressin.

Intestine

It is generally agreed that stimulation of the splanchnic nerves causes vasoconstriction in the intestine. As early as 1899, Bayliss & Starling (11) demonstrated that such stimulation decreased the volume of intestinal segments. Burton-Opitz (27) observed a reduction in mesenteric venous flow in etherized dogs without a significant increase in portal vein pressure, thus showing that mesenteric resistance was increased. Deal & Green (38) measured flow in the cranial mesenteric artery and the appropriate pressures in dogs anesthetized with pentobarbital in order to determine intestinal vascular resistance. Although their control flows were abnormally low (less than 0.1 ml/min g of tissue), they found an increase of 50 per cent in resistance during splanchnic stimulation. Both Celander (34) and Kock (91) determined venous outflow from jejunal loops in

vagotomized cats under pentobarbital or chloralose-urethane anesthesia and also found that splanchnic stimulation reduced the flow.

Bülbring & Burn (25) observed a reduction in intestinal volume in plethysmographic studies with etherized, adrenalectomized dogs and cats during stimulation. After administration of ergotoxine, the same procedure produced an increase in volume. Atropine did not block the dilation phase, and they concluded that the splanchnic nerves contained some noncholinergic vasodilator fibers as well as the vasoconstrictor elements. Deal and Green also found that the sympatholytic agent, Iliadar, sometimes reversed the constrictor effect of splanchnic stimulation and that atropine had no influence on the reversal. Folkow *et al.* (47) in their studies on cats concluded that the vasodilator fibers could not be adrenergic either and hence that there were probably no splanchnic vasodilators. They thought that the vasodilation seen during splanchnic stimulation after ergotamine or Dibenamine was probably due to relaxation of the intestinal smooth muscle.

The primary effect of both epinephrine and norepinephrine on the intestinal vasculature seems to be the same as that of splanchnic stimulation. Schwiegk (118) found epinephrine to decrease both arterial and venous flow in dogs anesthetized with chloralose. In cats, also anesthetized with chloralose, Clark (35) found that epinephrine in all concentrations reduced intestinal venous outflow. Folkow *et al.* (47) observed vasoconstriction in the cat with both epinephrine and norepinephrine, as also did Kock (91). Grayson's group (61-64), using a calorimetric method, demonstrated that both compounds produced vasoconstriction in the mucosa and muscle of human ileostomies and colostomies. Binit *et al.* (15) observed an increase in the resistance of the mesenteric arterial bed upon intra-arterial injection of epinephrine in the dog under chloralose anesthesia. Green and co-workers (38, 65) in their studies on mesenteric artery flow in dogs anesthetized with pentobarbital found that both compounds caused a several hundred per cent increase in resistance. Selkurt *et al.* (121) observed a reduced flow through artificially perfused, denervated ileal segments under the influence of both substances. Bohr *et al.* (19) used the Zweifach preparation of the rat mesoappendix to show that epinephrine and norepinephrine were both constrictors whether administered intravenously or topically. Although these workers found epinephrine the more potent compound, all the other investigators (47, 65, 91) who compared the

two substances in the dog and the cat found norepinephrine to be the more potent (see below).

Two groups of workers (65, 118) have observed a secondary increase in blood flow in the dog intestine following the primary vasoconstriction due to epinephrine administration, although in the cat, Folkow *et al.* (47) could find the constrictor effect only. Several studies (35, 47, 65) have shown that only vasodilation occurs with epinephrine if given after such substances as ergotamine, Dibenamine, or Ilidar. These same substances are capable of blocking the constrictor effect of norepinephrine but do not reverse it.

Not all the results of investigations of volume or weight changes of the intestine under the influence of epinephrine and norepinephrine agree with the findings on blood flow. Woods *et al.* (139), Goetz (57) and MacLean *et al.* (96) all found that epinephrine caused a primary reduction in volume followed by a secondary increase. The latter observed a decrease in weight with norepinephrine. Opposed to these are the observations of Bülbring & Burn (25), Goetz (57), with small doses, and Burn & Hutcheon (26) that epinephrine increased the volume of intestinal segments of dogs and cats. As Folkow (48) has stated, these discrepancies might well be explained by the possibility that the smooth muscle relaxing effects of epinephrine result in a decreased transmural pressure in the intestinal vessels which for small doses of the drug overbalance its usual constrictor effects. Aside from this possibility, it remains highly questionable whether or not intestinal vascular resistance changes can be deduced from variations in the volume of the organ.

The influence of the parasympathetic portion of the autonomic nervous system on the intestinal vasculature is not completely clear. Celander & Folkow (32) observed an increase in intestinal blood flow in the cat as a part of the depressor response to sinus nerve stimulation. Since this disappeared after ergotamine, they concluded that there were no dilator fibers involved and that the increase in flow was the consequence of a reduction in constrictor tone. The parasympathetic mediator, acetylcholine, does seem to cause vasodilation, as shown by the just-mentioned workers, as well as by Binit *et al.* (15) and by Bean & Sidky (13). The latter took great care to separate the effects of the compound on the vasculature and the visceral smooth muscle and showed that the increase in blood flow appeared before the augmentation of motor activity. The increase in blood flow was abolished or reversed by vigorous segmental contractions. However, one note

of caution should be made regarding all three of these studies. All were performed with perfused preparations and it may be that the control blood flows were abnormally low as is so frequently the case with perfused intestinal segments. Although adequate control data are not given in any instance, estimations from Bean and Sidky's results indicate that their preparations may have had an abnormally high constrictor tone. Care should be exercised, therefore, in concluding that acetylcholine has a dilator effect in the intact normally perfused intestine.

It seems reasonable to conclude that splanchnic nerve stimulation, and administration of the adrenergic substances, epinephrine and norepinephrine, produce vasoconstriction in the intestine, presumably by excitation of alpha adrenergic constrictor receptors as reviewed by Green & Kepchar (66a). The usual secondary dilation observed after epinephrine injection and especially the primary dilation seen when epinephrine is administered following Ilidar or ergotamine blockade indicates the presence of beta adrenergic dilator receptors as well. This offers an explanation of the lesser constrictor potency of epinephrine since this compound, unlike norepinephrine, stimulates both the constrictor and dilator receptors. The small increase in flow which occurs during splanchnic stimulation after administration of Ilidar or ergotamine seems more likely to be explained by intestinal smooth muscle relaxation, or by mechanical distention of blood vessels due to a rise in blood pressure, than by stimulation of the beta dilator receptors. It is highly questionable whether the vagus has any influence on the intestinal circulation other than that secondary to augmentation of motor activity. Acetylcholine probably has a dilator effect but unequivocal proof of this in the intact intestine is not available.

The influence of other chemical compounds on the intestine may be summarized as follows. Bülbring & Burn (25) found histamine to produce a slight vasodilation, as did Binit *et al.* (15). In this writer's laboratory, on the other hand, this compound has been found to produce constriction fairly consistently in artificially perfused intestinal segments. Both Selkurt's group (121) and Bohr and his colleagues (19) found serotonin to be an intestinal vasoconstrictor. The latter also found Pitressin to be a constrictor of intestinal surface vessels.

Vasodilation has been produced by isopropyl-norepinephrine in the hands of Green *et al.* (65), by curare in a study by Elwell & Bean (42), by adenosine

triphosphate in the investigations of Selkurt *et al.* (121) and of Binit *et al.* (15), and by topically applied procaine in Grayson's research (61) on human mucosal blood flow. Grayson also observed that cooling a limb caused dilation in the colostomy mucosa whereas heating the body produced constriction, the direction of the changes being opposite to those in the skin. Trapold (132) found that several ganglionic blocking agents caused a small decrease in resistance to flow in the mesenteric artery bed, although this must be interpreted in light of the fact that his control flows were abnormally low.

Sidky & Bean (12, 126) used their isolated intestinal segment preparation to investigate the effects of variations in the concentration of the respiratory gases in the perfusion fluid. They found that hypercapnia and hypoxia resulted in an increase in blood flow; hypocapnia resulted in vasoconstriction. Brickner *et al.* (22) determined the total mesenteric flow less that through the spleen in dogs breathing gas mixtures containing various percentages of CO₂. With less than 5 per cent CO₂, the circulatory changes were minor; at levels of 5 to 16 per cent, there was a significant decrease in mesenteric resistance.

Intestinal blood flow is profoundly influenced by motor activity. Anrep *et al.* (4) perfused loops of dog intestine and observed a decrease in venous outflow during muscular contractions. Sidky & Bean (127) in their studies of artificially perfused intestinal segments found that early in a contraction arterial inflow decreased and venous outflow increased, with venous pressure sometimes exceeding arterial pressure. If the contractions were rhythmic and of short duration, they could augment the flow. If the duration of a contraction was longer, the flow through the segment would decrease as a consequence of the fall in arterial inflow. As expected, these effects were more pronounced the stronger the contractions.

Lawson & Chumley (93) showed that increases in intraluminal pressure to values below 30 mm Hg caused a temporary decrease in blood flow followed by recovery to control values. At higher pressures only a partial recovery was noted. Recovery was not observed in segments placed in plaster casts or treated with procaine, and denervation was without influence. They concluded that the stretching of the gut wall initiated a vasodilation mediated through intrinsic nerve networks.

Selkurt *et al.* (121) have investigated the relation between blood flow through an artificially perfused denervated ileal segment and the arterial-venous pressure difference. They found the relationship to

be slightly curvilinear, convex toward the pressure axis, with a positive intercept on that axis of about 15 mm Hg. Since, as already pointed out, their observed flows at normal arterial-venous pressure differences were quite low, some caution must be exercised in applying their results to the normal situation. However, Johnson *et al.* (84) found a similar intestinal pressure-flow relationship in the totally perfused dog, although with higher flows for any given pressure.

Selkurt & Johnson (122) and Johnson (85) observed that the effect of increasing intestinal venous pressure was to produce a rise in vascular resistance in the mesenteric bed. They concluded that the resistance changes were not dependent on nervous mechanisms but suggested that the elevation of venous pressure induced a myogenic response in the resistance vessels.

Johnson (86) also investigated the influence on flow resistance of partial occlusion of an intestinal artery. In 70 per cent of the cases the resistance decreased with arterial pressure reduction. He concluded that this autoregulation of intestinal blood flow was not due to a local reflex but rather was the consequence of a myogenic response of the vascular smooth muscle.

Occlusion of the mesenteric artery also has an effect on the systemic circulation, causing a rise in arterial blood pressure. Sarnoff & Yamada (115) observed large increases in blood pressure in the cat and concluded that this effect was dependent upon reflexes initiated by receptors in the abdominal organs, particularly in the pancreas. In this species, they considered such reflexes more important than those originating in the carotid sinus and aortic arch. Boyer & Scher (20) observed smaller pressure changes in the same animal and concluded that there was no evidence for the presence of baroreceptors in the mesenteric artery, and that the rise in systemic arterial pressure was due only to mechanical diversion of the blood away from the abdominal viscera. Heymans *et al.* (79) performed similar studies with the dog and decided that the general blood pressure rise was a purely hemodynamic effect due to the exclusion of an important arterial vascular area and did not indicate the existence of abdominal baroreceptors. Selkurt & Rothe (123) performed similar studies in both dogs and cats. The results with cats agreed with the findings of Sarnoff and Yamada. Those obtained from dogs led the authors to conclude, in agreement with Heymans, that splanchnic baroreceptor activity in that species is slight.

Herrick *et al.* (78) measured blood flow through the cranial mesenteric artery of unanesthetized dogs with a thermostromuhr during treadmill exercise and found that the flow was essentially unchanged despite an increase in arterial blood pressure, indicating an intestinal vasoconstriction. Barcroft & Florey (9) observed exteriorized preparations of colonic mucosa of dogs during exercise. Early in the period mucosal pallor was evident but, as the exercise continued, the color returned to normal.

Several workers (50, 60) have attempted to study the influence of various emotional states such as depression, anxiety, fear, etc., on human intestinal blood flow by making inferences from observations on the degree of mucosal engorgement in colostomies. The possible errors inherent in such inferences have already been alluded to.

Pancreas

The information available on the influence of nervous stimulation and of drugs on pancreatic circulation is scanty. Both Anrep (3) and Gayet & Guillaume (52) showed a reduction in venous outflow as a consequence of splanchnic stimulation. The effect of vagal stimulation is not quite so clear. Anrep concluded that the vagus carried neither constrictor nor dilator fibers to the pancreas. Gayet and Guillaume consistently found a marked increase in blood flow during vagal stimulation.

Gayet & Guillaume (52), Maltesos & Watson (98), Jones (88), and Bennett & Still (14) all observed an increase in blood flow when secretin was administered, in contradistinction to Weaver (136), who could find no change in venous outflow. Jones found that the rise in flow was a function of splanchnic vasomotor tone and could be quite small when the tone was high. Because Bennett and Still observed a secretin-induced rise in blood flow only when the pancreatic duct pressure increased, they proposed that the apparent vasodilator action of the hormone was not due to a direct effect on the vasculature but was the consequence of a reflex initiated by the rise in ductal pressure during secretion. They concluded that a truly "vasodilation-free" secretin may be prepared.

Recently, Holton & Jones (80) used a photoelectric technique to measure blood content changes in the pancreas and found that acetylcholine, histamine, secretin, and pancreozymin all produce vasodilation, whether or not secondary to a rise in ductal pressure is not clear.

Spleen

In most of the investigations on the splenic circulation, attention has been directed toward changes in the volume of the organ rather than the blood flow through it. Adrenergic stimulation causes a marked decrease in volume in dogs and cats. As shown by Celander (33) in cats under chloralose anesthesia, sympathetic stimulation is more potent in this regard than epinephrine, which in turn is several times more effective than norepinephrine. Others, such as Ahlquist *et al.* (1) and Holtz *et al.* (81) have demonstrated that epinephrine is also more effective than norepinephrine in the dog. Many other compounds produce splenic contraction; ephedrine, pituitrin, histamine, acetylcholine, and amyl nitrite. Anesthetic agents also exert a profound influence; as shown by Hausner and co-workers (74), ether causes a reduction in size and various barbiturates a marked enlargement over that of the waking animal. Hahn *et al.* (72) reported that spleens taken from dogs anesthetized with pentobarbital weighed four times those from etherized animals. Almost any change in the environment which can produce a sympathetic discharge in the animal causes splenic contraction. Thus, Hargis & Mann (73) and Barcroft and co-workers (8, 10) observed this in waking dogs subjected to a loud noise, tail pinching, hemorrhage, exercise, or exposure to cold. The first mentioned workers thought that most of these responses were reflex, since they occurred so rapidly and were not observed after denervation. Barcroft and Elliott, however, did find contraction of the denervated spleen after a loud noise, although it was delayed and progressed slowly. One of the few maneuvers which increases splenic volume is feeding.

A number of investigators, for example, Glaser *et al.* (56), have concluded that the spleen is not an important blood storage organ in the human body, and hence does not change volume as markedly as in the dog or cat.

With regard to factors influencing the splenic blood flow, Burton-Opitz (28) found that stimulation of the splanchnic nerve or any of the fibers of the splenic plexus caused a reduction in blood flow through the splenic vein. Green and co-workers (67, 104) studied this in more detail and found that splanchnic stimulation of short duration decreased arterial inflow but temporarily increased venous outflow, thus accounting for the reduction in volume of the organ. They also

showed that epinephrine and norepinephrine had a similar effect, with the former being more potent. Phenoxybenzamine reversed the inflow reduction, and reduced the increase in venous outflow and the volume change. Acetylcholine and methacholine increased arterial and venous flow and slightly increased organ volume, these effects being blocked by atropine. This observation is in agreement with that of Hunt (83), but at variance with those of Ferguson *et al.* (45) and of Fleming & Parpart (46) who observed arteriolar constriction in the mouse spleen with topical application of acetylcholine as well as epinephrine, norepinephrine, and histamine. An extensive investigation by Grindlay and co-workers (69) with thermostomuhrs in unanesthetized dogs showed that a loud noise resulted in a temporary increase in venous outflow while having no effect on arterial inflow, thus accounting for the usual volume reduction of the organ. They also found that both arterial and venous flow rose after feeding and fell after hemorrhage in agreement with volume changes. During exercise both flows increased. Since splenic volume decreases during exercise, this provides a good example of the danger inherent in assuming that the direction of volume change of an organ indicates the direction of flow change.

Mesenteric Circulation as a Whole

The influence of nervous stimulation or drug administration on the mesenteric circulation as a whole must for the most part be inferred from a synthesis of the effects of these factors on the separate organs. Most studies in the intact animal have been on the total splanchnic flow with no separation of this into its hepatic arterial and portal venous components. Even where the portal flow is determined separately care must be exercised in the interpretation of the results, since the factor under study may alter the portal flow by affecting hepatic resistance and have no effect on mesenteric resistance. Only when measurement of the portal flow is accompanied by determination of the mesenteric arterial-venous pressure difference is it possible to infer the effects of the factor on the mesenteric circulation, and even then the effect may not be direct; for example, a passive dilation of mesenteric vessels due to a rise in portal venous pressure as a consequence of a hepatic resistance increase or the contrary myogenic vasoconstriction studied by Selkurt and Johnson. One such study in which pressures were recorded, al-

though mesenteric resistances were not calculated, is that of Katz & Rodbard (89). Another pertinent investigation is that of McMichael (99). The results of these workers are considered below with a summary of what seems to be the best evidence to the present time on the factors affecting blood flow through the separate mesenteric organs.

There is general agreement that splanchnic stimulation increases the resistance to blood flow through the mesenteric circuit. Most results indicate that the effect of norepinephrine and the primary effect of epinephrine are similar, with norepinephrine the more potent of the two except in the spleen. In general, epinephrine has a secondary dilator effect which is the only consequence of its administration following treatment with various sympathetic blocking agents. Katz and Rodbard, and McMichael found that epinephrine first increased then decreased mesenteric resistance. It might be noted that adrenergic stimulation may result in a temporary increase in portal venous flow despite the primary rise in resistance, because such stimulation evokes splenic contraction and the discharge of its stored blood.

Vagal stimulation probably has little if any significant influence on the mesenteric blood flow, except insofar as flow is changed secondary to an increase in motility in the stomach and gut. Because the results of studies with acetylcholine are contradictory with all organs except the intestine, and there their validity may be questioned, much the same conclusion must be drawn for this factor for the present.

Pitressin seems to have a constrictor effect in most of the mesenteric organs. Again the data of Katz and Rodbard, and of McMichael confirm this for the mesenteric circuit as a whole. Since serotonin seems to be a constrictor in the intestine, and since the major part of the mesenteric flow passes through this organ, the effect of this hormone on the circulation as a whole is probably the same. The influence of histamine on the gastric circulation seems to be dilatory; however, its effect on the other organs is not so clearly established. Katz and Rodbard's data indicate little change in the over-all flow resistance in the mesenteric organs under the influence of this compound; the dilation in the stomach may be balanced by constriction elsewhere. Finally, one physiological maneuver, exercise, seems to cause vasoconstriction in all the mesenteric circulation except in the spleen.

RELATION OF BLOOD FLOW TO FUNCTION
OF THE MESENTERIC ORGANS

The influence of the blood flow on the function of the mesenteric organs seems to be clearly established in only one respect; namely, that a certain minimum flow is essential for the maintenance of the integrity of the cells. Whether or not the alimentary activities, secretion, absorption, and motility, of the stomach, intestine, and pancreas require an augmentation of the blood supply above the basal level is the subject of conflicting evidence, although most of the admittedly scanty evidence indicates that, necessary or not, there is an increase in blood flow through these organs after the ingestion of a meal.

Herrick *et al.* (77), in thermostromuhr studies in the unanesthetized dog, observed that 1 to 2 hours after taking a meal the cranial mesenteric artery flow was increased to 50 to 60 per cent above control. Since there were increases of similar magnitude in flows through the femoral and carotid arteries at the same time, they concluded that digestion caused a general increase in cardiac output rather than a shift of blood supply from other regions of the body to the abdominal viscera. Reininger & Sapirstein (109) used their K^{42} method to demonstrate that there was a similarly uniform increase of about 30 per cent in blood flow to all parts of the body of the rat after feeding.

Brodie and co-workers (23, 24) measured the oxygen uptake by segments of canine small intestine and observed a 30 per cent increase during absorption of dilute salt solutions and a 60 per cent increase during absorption of protein solutions. They reported similar rises in blood flow, but this must be interpreted in light of their use of the plethysmograph to make the measurements. Lindseth (95) determined both total intestinal segment flow and its partition among the individual tissues in anesthetized fasted and fed dogs. In upper jejunal segments, feeding produced no significant change in total venous outflow but caused a diversion of the flow through the mesentery to the capillaries of the mucosa and submucosa. In the ileum, there was a 25 to 30 per cent increase in total flow, almost all of which went to the muscle, there being essentially no change in that through the absorbing mucosa. He also found no significant alteration in the fraction of the total flow which passed through arteriovenous anastomoses.

Numerous attempts have been made to determine the relation between blood flow and secretion by the

gastric mucosa. Thompson & Vane (131) in their studies with the perfused cat stomach observed parallel changes in secretory rate and blood flow as a consequence of sympathetic stimulation, epinephrine administration, and celiac arterial infusion of histamine, and concluded that secretion could be directly influenced by changing blood flow. Lim *et al.* (94), on the other hand, in similar studies with the dog found that histamine-induced secretion could occur in face of a falling blood flow. Further, sodium nitrite increased the blood flow without initiating secretion. Cutting *et al.* (37) observed increases in both parameters in the cat when given histamine or pilocarpine. Pituitrin decreased blood flow and volume secretion but had little if any effect on the amount of acid produced. Warming the stomach or the administration of erythrol tetranitrate increased flow without stimulating secretion. Finally it has been noted that vagal stimulation which induces secretion has little or no effect of the total blood flow through the stomach although it does cause mucosal engorgement. There seems little doubt that the parietal cells must require an increase in oxygen supply during secretion. There are, however, a number of ways by which this can occur without alteration in the total gastric blood flow. Oxygen extraction can rise, although the work of Peters & Womack (105) indicates that such is not the case in the dog in response to histamine injection or vagal stimulation. Other possibilities include shifts of flow from arteriovenous anastomotic channels, from other tissues, or from other regions of the stomach to the fundic mucosa. Experiments to measure the distribution of blood flow to the different tissue and arteriovenous channels in the basal and in the secretory states are needed. It is the mucosal flow that is of real significance and it may not vary in the same manner as the total flow. On the basis of the evidence presently available reasonable conclusions seem to be that agents which decrease gastric blood flow below the basal level prevent or at least markedly reduce secretion, that increased blood flow does not of itself initiate or augment secretion, and that whether or not secretion is necessarily accompanied by an increase in total gastric blood flow cannot be answered definitely.

The investigations on the relation of pancreatic secretion to blood flow have been critically reviewed recently by Tankel & Hollander (130). They pointed out the contradictory nature of the evidence presently

available and stated that it does not warrant the conclusion that pancreatic secretion is dependent on the blood supply, except that a minimum flow is required to maintain cellular activity and provide fluid for secretion.

The relation between motor activity and blood flow in the stomach and intestine have been referred to earlier. Vigorous contractions, such as are produced by vagal stimulation, cause a reduction in blood flow. On the other hand, a reduction in blood flow may, as suggested by Celander (34), be re-

sponsible for the usually observed inhibition of motility during sympathetic stimulation.

The best general conclusion seems to be that there is as yet no clearly established demonstration that the mesenteric organs need an augmentation of their basal blood supply to perform their alimentary function. It seems clear that these organs receive their proportionate share of the general rise in cardiac output which follows feeding, but whether this is coincidental or to satisfy an essential requirement is debatable.

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The renal circulation

EWALD E. SELKURT

*Department of Physiology, Indiana University
School of Medicine, Indianapolis, Indiana*

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THE INTRODUCTION of the concept of the counter-
 current osmotic multiplier system to the kidney by
 Wirz *et al.* (345-349) as a means of explaining
 urinary concentration and dilution has apparently
 initiated a phase of re-evaluation of classical renal
 functional concepts which promises to be far reaching
 in scope. Recent critical reviews, while pointing out
 gaps in our knowledge, have nevertheless opened up
 exciting vistas and new pathways for research (169,
 171, 289, 314). The countercurrent concept rests
 rather firmly on findings in the rat and hamster;
 however, significant anatomical differences in the
 kidneys of the dog and man require that this hypoth-
 esis be intensively tested in these and other species.
 Only about one-eighth of the nephrons of the human
 kidney appear to have the long medullary loops of
 Henle requisite for the mechanism (245). Most lie in
 the cortex, and have straight, short, thin segments, or
 indeed, none at all (fig. 1). The dog, however, has
 long loops and long, thin medullary segments, yet
 its kidneys are not remarkably different from those of
 the human in concentrating power.

The renal circulation has been found to play a
 unique and important role in the composite picture of
 the countercurrent mechanism. Knowledge of the
 distribution of blood to the cortex and medulla has
 assumed pre-eminent importance. Older ideas have
 had to be revised. The vasa recta, considered originally
 as a medullary shunt by Trueta *et al.* (311), assume

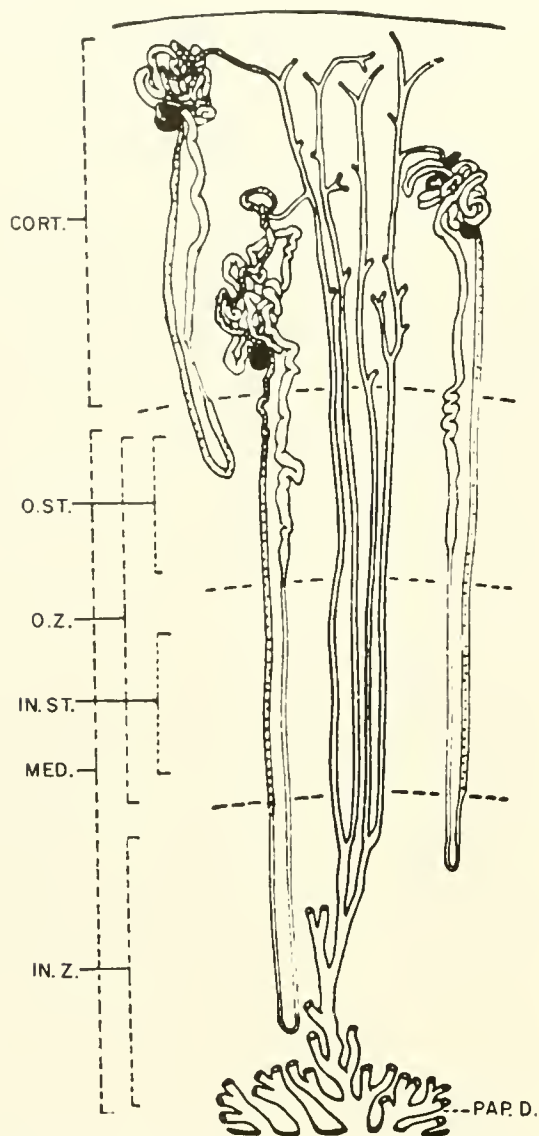


FIG. 1. Anatomical distribution of nephron types in the human kidney. CORT.: cortex; O.ST.: outer stripe or band; O.Z.: outer zone of medulla; IN.ST.: inner stripe or band; MED.: medulla; IN.Z.: inner zone of medulla; PAP.D.: papillary duct. [After Peter (245).]

new importance as the vascular counterpart of the countercurrent system of the nephrons. Longley *et al.* (191) look upon the vasa recta as *retia mirabilia conjugata* (similar to the *retia mirabilia* of the swim bladder of fishes), especially endowed to function as a countercurrent multiplier system. Recent studies (166, 309) have shown that the flow of blood through these vessels appears to be significantly slower than through the cortical circulation, apparently a functional adaptation to the optimal operation of the countercurrent mechanism.

The question of the possible role of the phenomenon of the autoregulation of the renal circulation in the countercurrent system has been raised. Speculatively, it would appear undesirable for rapid fluctuations in blood flow to occur through the zone of hypertonicity, and the over-all constancy of renal blood flow may thus be an adaptation to insure stability in this system.

This article will include largely the developments in renal circulatory physiology since Homer Smith's review in 1940 of *The Physiology of Renal Circulation* (286). This era has seen the ascendancy of the clearance method for measurement of renal blood flow, the waxing and waning of the Trueta juxta-medullary shunt mechanism, the development of a growing interest in the mechanism of renal circulatory autonomy, and the unfolding of the countercurrent hypothesis of kidney function with important implications for the renal circulation.

FUNCTIONAL ARCHITECTURE OF THE RENAL CIRCULATION

Limitation of space precludes the consideration of the anatomy of the renal circulation on the broad comparative basis that it warrants. Rather, major emphasis will be placed on the salient features of circulation in the dog, the species in which a significant proportion of the functional studies have been made, with appropriate references to other species, especially human, when needed for full development of a given topic.

Arterial System

Major distribution of the renal artery in the dog is shown in figure 2 [from plastic injection corrosion studies of von Kügelgen *et al.* (322)]. Figure 3 shows division of the interlobar artery into primary, secondary, and tertiary arcuate arteries, from which spring the interlobular arteries. The afferent arterioles usually supply only one glomerulus, but rarely may branch to supply 2 to 4 glomeruli with a total of 200,000 per kidney. This is compared to estimates ranging from 600,000 to 1,700,000 in each human kidney (213, 216, 318).

SPECIALIZED ARTERIAL CIRCUITS. Spanner (290, 291), Trueta *et al.* (311), Baker (6), and von Kügelgen & Passarge (323) have found peculiarly coiled vessels (which arise from the interlobar arteries) in the renal sinus of dog, cat, and human. These spiral vessels,

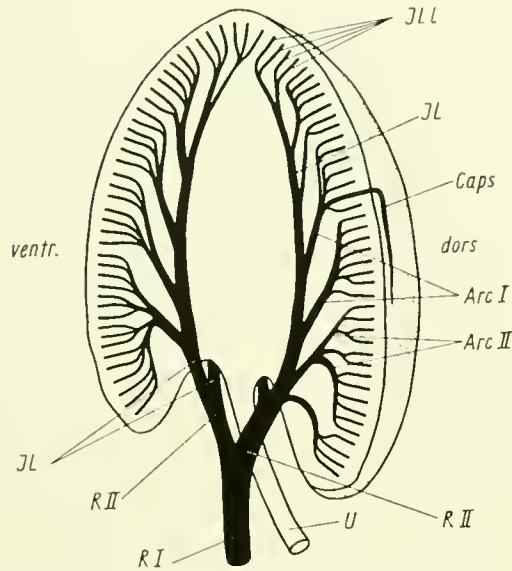


FIG. 2. Horizontal section through the dog kidney. *RI* and *RII*: renal artery and primary branches; *Arc I* and *Arc II*: primary and secondary arcuate arteries; *IL*: interlobar artery; *JLI*: interlobular artery; *Caps*: capsular artery; *U*: aorta. [After von Kügelgen *et al.* (322).]

100 to 150 μ in diameter, form a plexus which supplies the calycine mucosa and the renal papilla (fig. 4). Baker contends that they anastomose with the vasa recta. It is important to emphasize that these vessels participate with the vasa recta system (vide infra) in supplying blood to the papillary zone containing the tips of the loops of Henle, the site of maximal osmotic concentration. Their long, coiled length delivers blood into the vasa recta system at low pressure (6). Arterio-arterial anastomoses occur in this system, an exception to the usual pattern of end arteries found in the divisions of the renal artery.

Venous System

Deferring discussion of the glomerular and capillary circulation, attention is directed to the venous system in figure 5. Note the sparsity of interlobular veins relative to the interlobular arteries (a ratio of 20 to 1). Their function appears to be to connect the superficial and deep venous systems of the cortex (*V. corticalis superficialis* and *V. corticalis profunda*), into which the capillaries drain. The upper fifth of the cortex appears to be an "arterial-free" zone (*af* in fig. 5), so that the upper glomeruli are overlaid by only venous channels (stellate veins, superficial cortical veins), and pre-venous capillaries (cortex corticis). Puncture of glomeruli for this reason has been unsuccessful in the dog. A "venous-free" zone (*vf*) also exists, free of cortical veins (superficial and deep), and occupied only by occasional interlobular veins.

VENOUS SINUSES; VENO-VENOUS ANASTOMOSES. Venous sinuses or sinusoids lying in the connective tissue adjacent to the pelvis of the human kidney were observed by Spanner (290, 291) and by Barrie *et al.* (12). Spanner described them as isolated accumulations of large venous plexi arranged superficially along the walls of the minor calyces of the renal pelvis. Trueta *et al.* also described in the same zone of the human kidney many vessels of large caliber which unite interlobar veins (veno-venous anastomoses). These vessels lie closely adjacent to the outer surfaces of the walls of the calyces of the renal pelvis, and the capillaries of the pelvic mucosa drain into this complex system. They may offer a clue to the phenomenon of pyelovenous backflow sometimes seen after retrograde pyelography. Veno-venous anastomoses

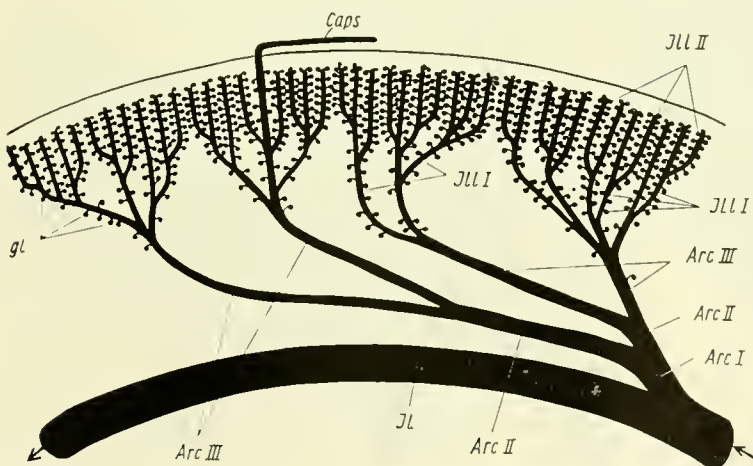


FIG. 3. Scheme of the finer arterial supply of the dog kidney. *gl*: Glomerulus with afferents. [After von Kügelgen *et al.* (322).]

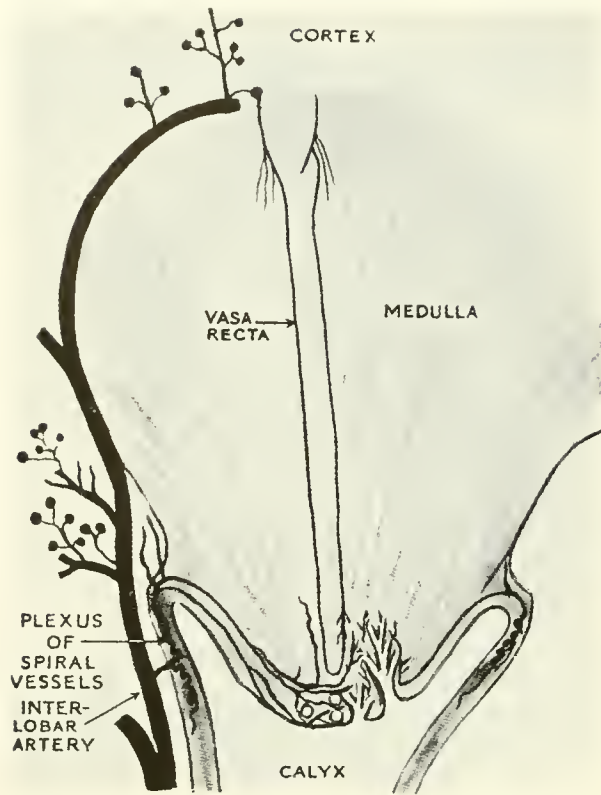


FIG. 4. The medullary and papillary blood supply of the kidney. [After Baker (6).]

are common in the dog kidney between interlobar veins, between arcuate veins, and between stellate and arcuate veins (322).

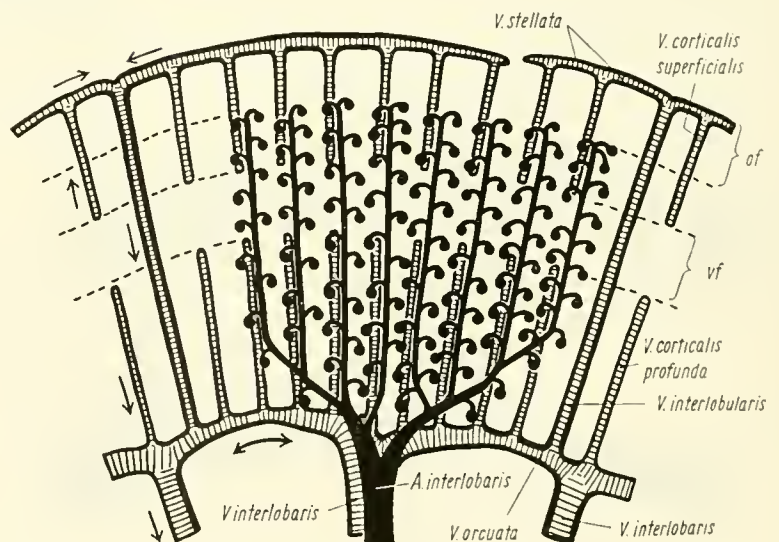
ARTERIOVENOUS ANASTOMOSES. The venous sinusoids have been described as the site of numerous arterio-

venous anastomoses in the human kidney by Spanner. Barri \acute{e} t *et al.* (12) believe that such arteriovenous connections occur between the aforementioned spiral arteries and the sinusoids, the latter emptying presumably into the interlobar veins, but admit that open communications between the spiral arteries and the sinusoids are extremely difficult to demonstrate. Trueta *et al.* have disputed Spanner's findings, and Baker (6) found only an insignificant number in confirmation of Trueta. Nor could von K \ddot{u} gel \acute{e} n *et al.* (322, 323) and Christensen (54) find them in the dog kidney.

In summary, arterio-arterial and veno-venous anastomoses occur commonly in the kidneys of man and dog. Although arteriovenous anastomoses probably exist, their occurrence is infrequent. Functionally, direct A-V shunting of blood must therefore be negligible, and blood passes generally through a capillary circuit (cortical peritubular plexus or medullary vasa recta system). In confirmation, Piiper & Sch \ddot{u} rmeyer (249) found that the intact dog kidney passed only 1.5 per cent of 19 μ wax spheres injected into the renal artery, 0.3 per cent of 30 μ , and 0.08 per cent of 38 μ size. Denervation, and injection of KCN, novacaine, and histamine did not influence the results. Although Simkin *et al.* (283) recovered glass spheres up to 440 μ in size from the renal vein of excised human kidneys, they did not indicate what portion these represented of the total injected.

VENOUS VALVES AND VALVELIKE STRUCTURES. These have been described by von K \ddot{u} gel \acute{e} n *et al.* (320-322) in the dog, swine, and human kidney. They are

FIG. 5. The blood supply of the cortex, including the venous system. af: Arterial-free zone of the cortex; vf: vein-free zone of the cortex. [After von K \ddot{u} gel \acute{e} n *et al.* (322).]



located in the renal vein at its entrance to the vena cava, and in the main branches of the renal vein (the latter not as a rule in man). They are found also at the orifices of the interlobar veins, arcuate veins, and occasionally just before the opening of the capsular (stellate) veins into the interlobular veins.

Koester *et al.* (162) have found, in both human and dog kidneys, structures in the veins which might act as effluent constrictions, which they described in terms of "stenoses" and "sinusoidal cushions." Stenoses are common at the ostia of smaller tributaries entering interlobar veins in the human kidney. They seem to be composed of a dense collagenous framework lined with endothelium; usually muscle is present as a proliferation of the media of the vessel. In the dog, stenoses appear occasionally along the course of the interlobars and primary tributaries to the renal vein; however, they are present primarily at the confluence of arcuates with interlobars and of the interlobulars with arcuates.

At the confluence of arcuates with one another to form an interlobar vein in the human kidney, the sinusoidal cushions usually appear, sometimes at the confluence of the interlobulars with arcuates. These structures characteristically contain venous sinuses (which connect with interlobular and medullary veins) in the connective tissue matrix. These structures are often interlaced with smooth muscle. Their appearance is said to resemble erectile tissue (162). In the dog, they are less extensive and lie primarily close to the arcuate-interlobar junction. Smooth muscle in the cushions of this species is very inconspicuous or absent.

It is worthy of emphasis that the aforementioned structures are not valves in the sense of those found in systemic veins, although many of those pictured by von Kügelen *et al.* (320, 321) exhibit a cusplike organization. In any event, their designation as "effluent constrictors" at present best describes their function, although the functional significance is hard to assess. The relatively high pressure found in the arcuate veins of dogs (24 mm Hg) by Swan *et al.* (302) appeared to give functional evidence of a point of increased resistance at the arcuate-interlobar junction. When the catheter was withdrawn into the interlobar vein, pressure decreased immediately to 7 mm Hg. Brun *et al.* (41) found wedged catheter pressures averaging 18 mm Hg in the human kidney; the pressure in the renal vein averaged 5.6 mm Hg. It was concluded that the wedged renal vein pressure equalled arcuate venous pressure and hence very near to the pressure in the peritubular capillaries and

interlobular veins. According to Koester *et al.* (162), the effluent constrictors keep the kidney "functionally distended" with fluids; they state also that these structures cause smaller vessels of the vascular system (venous channels?) to widen in bore, reducing resistance to blood flow. The logic of this can be doubted since this at best would only compensate for the initial resistance imposed. Nor is this supported by physiological studies in which venous pressure has been experimentally elevated (119, 122, 123, 233, 273, 281, 329), under which circumstance over-all renal resistance in fact increases, possibly by a "venous-arteriolar" reflex.

Glomerular Circulation

The studies of Boyer (29), Elias *et al.* (82), Hall (125, 126), Johnston (154), and Kurlz & McManus (170) show that the glomerular capillaries are not simple loops, but form a freely branching, anastomotic network (fig. 6). More specifically, larger through channels exist with an associated capillary network of smaller anastomotic channels. Hall has suggested that this may afford a structural basis for the skimming of plasma relatively freed of cells into the network of small capillaries, while the greater mass of blood cells directly and rapidly flows through the lobule to the efferent arterioles as an axial stream.

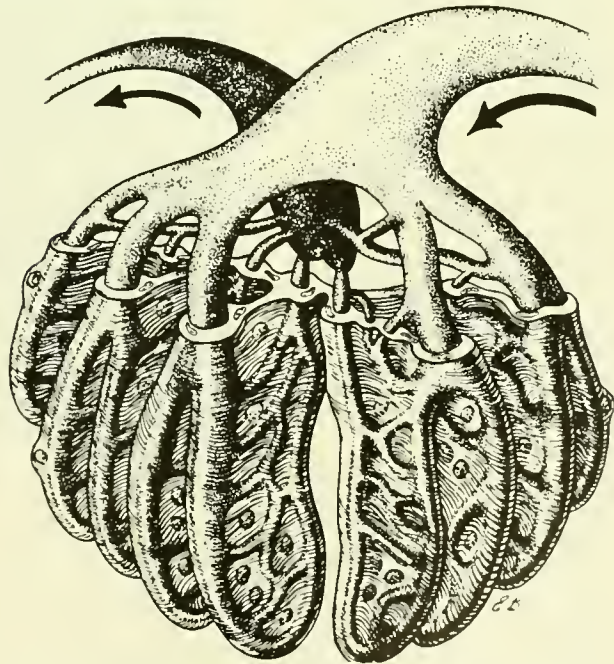
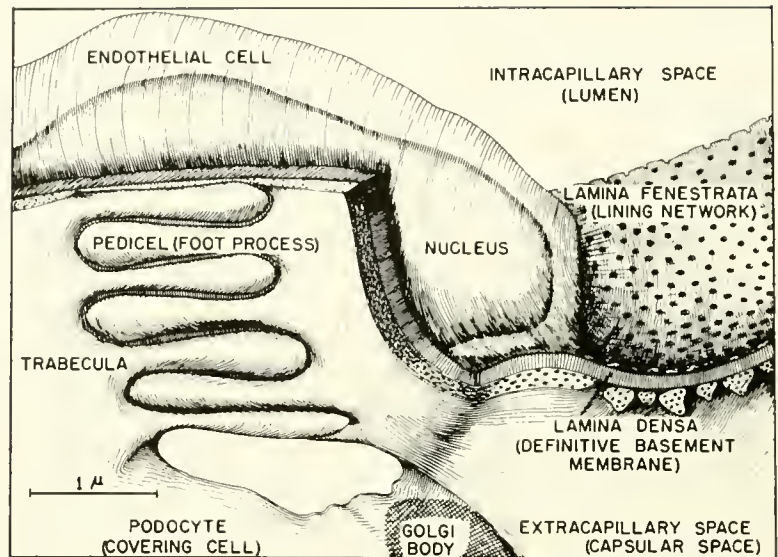


FIG. 6. Glomerular capillary supply, showing anastomotic connections. [After Elias (82).]

FIG. 7. Electron microscope reconstruction of the glomerular filtering membranes. [After Hall (125).]



This may facilitate the filtration process by slowing flow and reducing turbulence.

Figure 7 shows a sectional diagram of the structures forming the filtration apparatus as developed by electron microscopy (125). The pores in the capillary endothelium (0.05μ thick) (lamina fenestrata) are too large (0.1μ) to restrain the plasma constituents. Rather, they expose the ultrafiltration membrane, the lamina densa, to the free flow of plasma by removing the endothelial cytoplasmic barrier.

Although the lamina densa (glomerular basement membrane), 0.1μ thickness, exhibits differences in stratification (244), it is probable that it is a homogeneous layer; pores that have been noted are probably artifactual. It appears to be the limiting membrane for restraint of plasma proteins and cells.

The podocytes (foot cells) of the visceral layer of Bowman's capsule rest on the lamina densa with thousands of foot processes (pedicels). Hall has suggested that they may play an important part in the regulation of filtration. The space between the pedicels may be narrow enough (100 \AA) to be a limiting dimension in restriction of plasma proteins ("slit pore"). Hall suggested that the foot processes may be narrowed or widened thereby exposing a greater or lesser area of basement membrane, although a mechanism by which such changes could be brought about has not so far been proposed. However, it is conceivable that changes in caliber of the capillaries as a function of internal pressure (*vis a tergo*) may alter the spacing of the pedicels. Using as a basis the observations on the frog glomerulus, Elias *et al.* (82) described another possible method of regulation. They observed that

the position of the glomerular blood channels is not constant and undergoes changes (e.g., transverse displacement) in relation to the foot processes. Thus, a group of pedicels may be active while a blood channel is located under them, and later at rest (when that blood channel has shifted to a new location).

The permeability of the filtering membrane of the kidney has been repeatedly studied by determining the renal plasma clearance of molecules of varying sizes. Wallenius (326), for example, by fractional hydrolysis of dextran, produced and separated substances with a wide range of molecular sizes and shapes and examined the facility with which they passed into the urine (fig. 8). He calculated that the pore radius in the dog glomerular membrane may range from 18 \AA to 50 \AA . These findings are in accord with the anatomical evidence. The findings of Giebisch *et al.* (100) are in essential agreement. The ratio of dextran clearance to circulation clearance fell markedly at a molecular weight of ca. 50,000.

Juxtaglomerular Complex

Two structural entities at the vascular pole of the glomerulus, the juxtaglomerular apparatus and macula densa, have been thought to be related in some way to the control of blood pressure or salt balance and thus to be concerned with renal hypertension (310). One of these, the juxtaglomerular apparatus (JGA), is a thickening of the media of the afferent glomerular arterioles (polkissen) (fig. 9). The cells of the JGA become swollen, afibrillar in

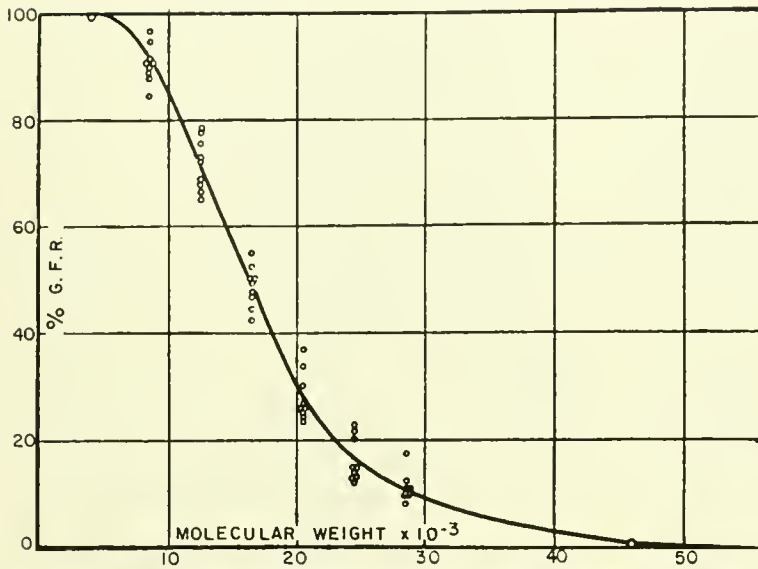


FIG. 8. The relationship of the molecular weight of dextran to percentage filtered. [After Wallenius (326).]

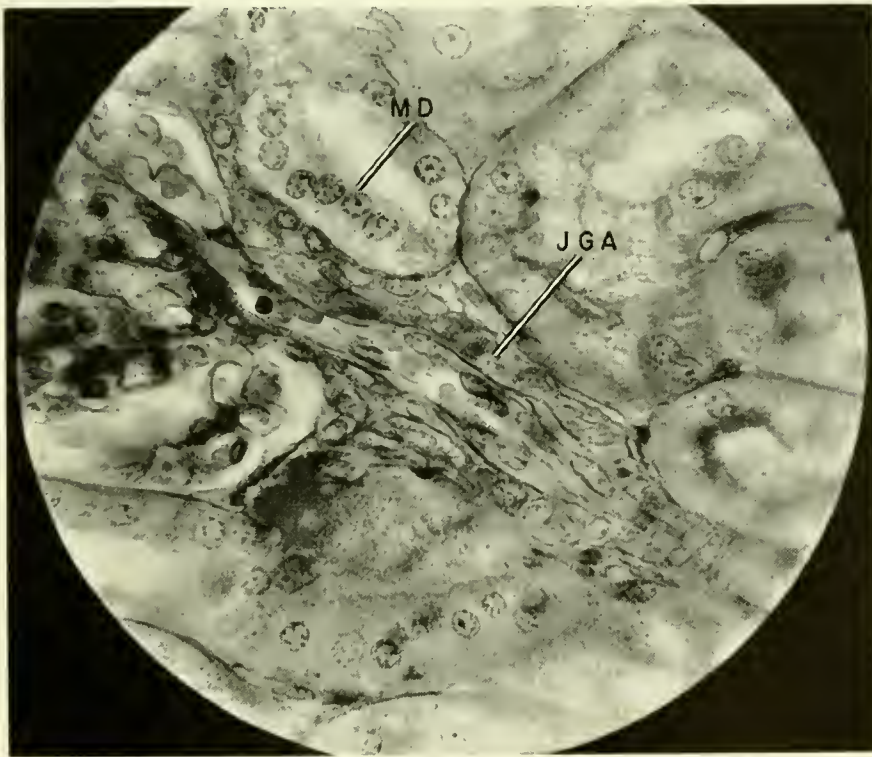


FIG. 9. The juxtaglomerular complex of the kidney. *JGA*: juxtaglomerular apparatus (Polkissen); *MD*: macula densa of distal convoluted tubule. [Courtesy of B. S. Garber (unpublished).]

appearance, and contain granules (periodic acid-Schiff reaction) which vary in amount in various forms of experimental hypertension and with variations in sodium intake. Pathological states which produce renal ischemia, such as the crush syndrome, cause similar changes and are accompanied by increase in blood pressure (110). A role in the regulation of autonomy has been invoked for this structure (121,

274, 281, 308, 330). In general, when the kidney is exposed to hypertensive blood pressures, the granularity decreases; if the blood pressure is decreased, the granularity tends to increase. Tobian (310) feels that these cells act as "stretch receptors," changing their rate of secretion inversely with degree of stretch of the walls of the arterioles.

The changes in granularity in the JGA cells are

related to extractable renin or its precursor. It is now conceived that renin is an inhibitor of an antihypertensive function of the kidney (163). An explanation of hypertension caused by renal ischemia would be as follows: if the renal artery is constricted, the JGA cells, being stretched less, would increase the secretion of renin. This would then inhibit the cells subserving the antihypertension function of the kidney, and systemic blood pressure would rise.

The cells are also influenced by electrolytes. A diet low in sodium increases granulation in dogs, cats, and rats (both intact and hypophysectomized). Increase in salt intake decreases granularity (310). Although a complex interrelationship with the adrenal cortex is probable, a simpler explanation offered by Tobian is that a low salt intake favors a decrease in blood volume, reduced blood pressure, and decreased stretch of the JGA cells (increased secretion). A high salt diet would have the opposite effect. On the basis of the above scheme, a decreased sodium diet should ultimately result in increased blood pressure, based upon the increased granularity of the JGA. This may indeed be a compensatory mechanism to maintain blood pressure in the face of lowered blood pressure resulting from decreased plasma and extracellular volumes caused by low sodium intake.

The other structure of importance is a portion of the distal convoluted tubule near the vascular pole, the macula densa. McManus (194-196) has suggested that the JGA, macula densa, and associated structures be together called the juxtaglomerular "complex." This epithelial plaque appears to have a reversed polarity from the rest of the tubule, in the sense that the Golgi apparatus is between the nucleus and the attached pole of the cell, (contiguous to the vasculature), rather than between the nucleus and the lumen. The suggestion made by McManus (196) and supported by Garber *et al.* (98) was that these cells abstracted from the contents of the lumen and transmitted this material to the cells of the arterioles. It is relevant to point out that a site of active sodium reabsorption is found in the vicinity of the distal convoluted tubule. It has been suggested that the JGA and macula densa form a regulatory system capable of responding to osmotic pressure changes (and possibly hydrostatic pressures), in turn modifying glomerular filtration in a self-regulatory manner. This interesting hypothesis needs experimental verification, particularly in view of the contention by de la Peña & de Castro (70) that structures resembling the macula densa were found in apposition to efferent arterioles in the human kidney. It is worthy

of note that afibrillar cells containing granules, similar to those in the afferent arterioles, have been noted in efferent arterioles (194).

Blood Supply to the Medullary Zones

Edwards (79) has described two types of efferent arterioles which exist in the juxtamedullary zone of the human kidney. One out of four to five glomeruli has a "corticomedullary" efferent arteriole to capillaries of the juxtamedullary parenchyma (fig. 10). The others (about 180,000 per human kidney) have long, descending arterioles (arteriolae rectae spuriae). These go on to the capillaries. One type forms networks around the tubules, the other goes on to the vasa recta system (fig. 11). The venae rectae return to the arcuate veins.

Note in table 1 the greater total muscle volumes in the medullary efferent arterioles as compared with the cortical. The total volume of muscle in the wall of the afferent and efferent arterioles was 0.124 ml and in the medulla 0.169 ml (79). Christensen (54) found the diameters of the juxtamedullary vasa efferentia of the dog kidney about the same as those in the cortical vasa efferentia, contrary to the findings of Trueta *et al.* (311) who state that the caliber of the juxtamedullary efferent arterioles greatly exceeds the

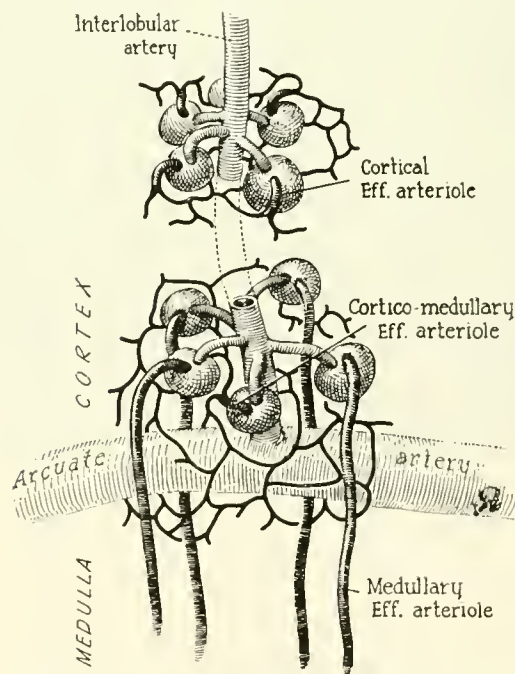


FIG. 10. The blood supply of the juxtamedullary zone. [After Edwards (79).]

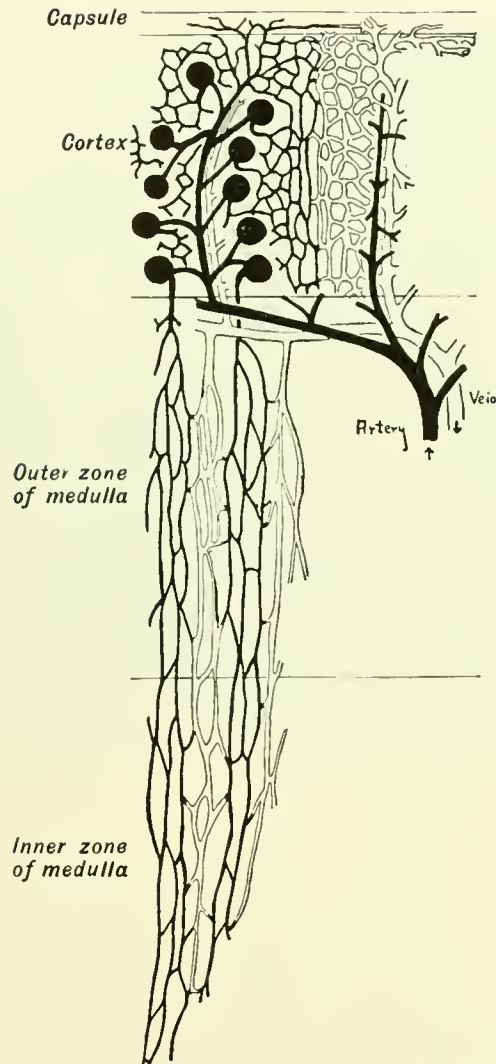


FIG. 11. The vasa recta system of the kidney. (Courtesy of A. A. Maximov & W. Bloom, *Textbook of Histology*. Philadelphia: Saunders, 1957.)

cortical efferents. The impression is definitely gained that the arterioles supplying the medullary zone are not low-resistance vessels as originally suggested by Trueta, but appear to be sites that could offer considerable resistance to blood flow, thus resulting in a significant drop in pressure gradient. One would anticipate on this basis that hydrostatic pressure in the vasa recta system would be very low were it not for the relatively high venous pressure found in the arcuate veins. Gottschalk & Mylle (112) and Wirz (347), by direct puncture of cortical peritubular capillaries in the rat, found an average of ca. 16 mm Hg (range: 14.0 to 20.0 mm Hg), which is well below the oncotic pressure of the plasma protein when one considers that glomerular filtration concentrates the protein. If this applies to the vasa recta, it would be favorable for optimal operation of the countercurrent system. The water abstracted from the collecting ducts moves into the vasa recta because of the gradient of chemical potential established by the colloid osmotic pressure of the plasma proteins.

Direct connections from the arcuate arteries into the medullary zone (arteriolae rectae verae) have been found in dog and man (18, 54, 217, 221, 311) but appear to be rare. Likewise, Ludwig's arterioles, branches from the afferent arterioles in the cortico-medullary zone passing directly into the medullary peritubular capillaries, are very infrequent in the dog, cat, and man. They are very rare (295) in the rat kidney. Oliver (236) and More & Duff (217) did not find them in normal human kidneys.

Renal Lymphatic System

A greater lymphatic system (cortical) exists, and there is a lesser (medullary) system which follows the

TABLE 1. Averaged Measurements in Microns of Cortical and Medullary Arterioles per Kidney and the Total Volume in cm^3 of the Muscle Composing Their Walls¹

| Arteriole | Total No. | Length per Arteriole | Total Length | External Diam. | Luminal Diam. | Total Muscle Vol. in cm^3 |
|----------------|-----------|----------------------|--------------|----------------|---------------|------------------------------------|
| <i>Cortex</i> | | | | | | |
| Afferent | 1,000,000 | 277 | 277,000,000 | 26 | 13 | 0.11 |
| Efferent | 820,000 | 200 | 164,000,000 | 16 | 12 | 0.014 |
| <i>Medulla</i> | | | | | | |
| Efferent | 180,000 | 600 | 108,000,000 | 33 | 18 | 0.065 |
| 1st brs.-3 | 540,000 | 400 | 216,000,000 | 24 | 14 | 0.064 |
| 2nd brs.-6 | 1,080,000 | 300 | 324,000,000 | 15 | 9 | 0.04 |

¹ Specimen calculation such as was used to obtain the muscle volume given in the last column of the above table.

Afferent arteriole: $\pi \times 13^2 \times 277,000,000 = 147,087,000,000 \mu^3 = \text{total volume}$

$\pi \times 6.5^2 \times 277,000,000 = 37,118,000,000 \mu^3 = \text{lumen volume}$

Total volume less lumen volume = $109,969,000,000 \mu^3 = 0.11 \text{ cm}^3$

[After Edwards (79).]

course of the vasa recta (251). They begin blindly in two locations: closely adjacent to the capsules of cortical glomeruli and beneath the mucosa of the papilla (fig. 12). The cortical lymphatic capillary networks do not have a functional relationship to the glomeruli. There is apparently no entry (248).

The lymphatics from the cortex with an interlobular course drain toward the arcuate vessels. Those from the medulla, draining the vasa recta, join the cortical branches at the arcuate level, then pass out with the interlobar vessels toward the renal pelvis. After converging at the hilum of the kidney, they course as perivascular channels to the cysterna chyli and thoracic duct (230, 261). Valves appear to be lacking in the lymphatics of the renal parenchyma but are present in the large trunks of the renal sinus.

Figures for the volume of lymph produced by the

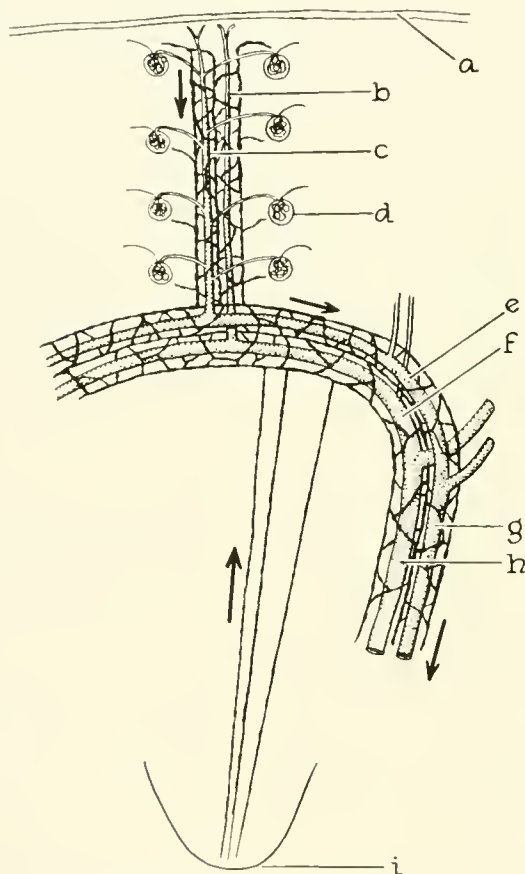


FIG. 12. The black threadlike lines indicate the greater and lesser lymphatic systems of the human kidney. The arrows show the probable direction of lymph flow; *a*: capsule; *b*: interlobular vein; *c*: interlobular artery; *d*: glomerulus; *e*: arcuate artery; *f*: arcuate vein; *g*: interlobar artery; *h*: interlobar vein; *i*: papilla. [After Rawson (251).]

kidney are scarce. Single capsular lymphatics of the dog yield flows of ca. 1 ml per hour (176, 177, 304). An estimate from the data of Schmidt & Hayman (266) yields a total of ca. 7 ml per hour per kidney.

Available anatomical evidence indicates that the capsular lymphatics join with the cortical and medullary lymphatics. Lymph flow increases when the kidney is subjected to osmotic diuretics (106, 230, 266). It is enhanced by ureteral obstruction. Pyelolymphatic backflow is evidenced by the fact that dye has been shown to move from the pelvis into the lymphatics with increased intrapelvic pressure. Elevation of renal venous pressure in the dog by 14 to 35 cm results in approximately 3-fold to 5-fold increase in lymph flow (123, 177). Marked increase in lymphatic pressure accompanies venous obstruction (157). Elevation of arterial pressure does not markedly increase lymph flow from hilar vessels: 0.023 ml per min at 58 mm Hg to 0.039 ml per min at 157 mm Hg (124).

It is of considerable interest that the lymph is high in sodium, chloride, and urea content compared to plasma and thoracic duct lymph (176, 304). LeBric & Mayerson (176) have found Na and Cl concentrations of 162 and 140 per liter, respectively, compared to 145.7 and 110.5 in the plasma, and 145.6 and 121.3 in the thoracic duct lymph. Interestingly, the K content does not differ significantly. These findings support the countercurrent hypothesis, for it is to be expected that these concentrations will be elevated as a result of the contribution of the medullary lymphatics which drain the papillary zone of hyperosmolarity of the kidney. K is not a significant contributor to this hyperosmolarity (267). This is further supported by the low glucose content of this fluid relative to plasma (304), suggesting an important source beyond the proximal convoluted tubules. An interesting avenue of investigation of the countercurrent mechanism thus appears to be afforded by a study of the renal lymphatics.

The renal lymph protein concentration averages 2.9 g per 100 ml as compared to 5.83 g per 100 ml for the plasma proteins (177). Evidently the renal lymphatics subserve an important function for operation of the countercurrent system by draining off excessive protein filtered by the vasa recta, which might otherwise accumulate in the interstitial spaces of the medulla. Removal of such protein would act to maintain a more favorable gradient of movement of interstitial fluid into the vasa recta, attracted by the relatively higher oncotic pressure.

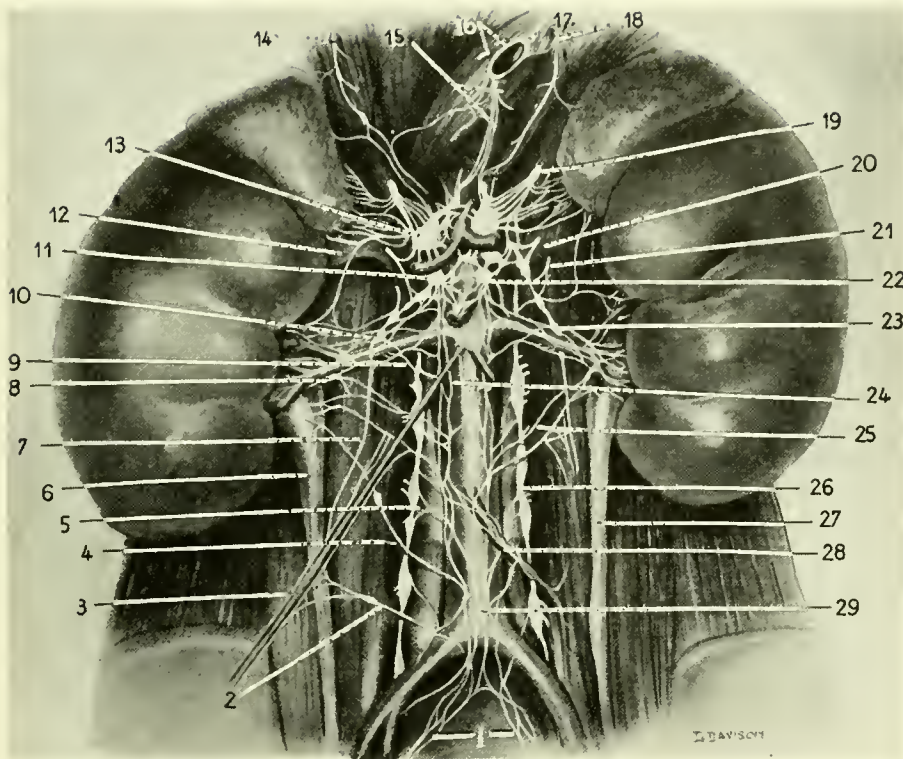


FIG. 13. Renal plexuses of the human kidney, anterior aspects. 1: Hypogastric nerves. 2: Middle spermatic and ureteric nerve. 3: R. spermatic artery. 4: Renal branch from sup. hypogastric plexus. 5: Lumbar splanchnic nerve. 6: Sup. ureteric nerve. 7: Communication between renal plexus and spermatic nerve. 8: Small renal ganglion. 9: Renal branch from lumbar sympathetic trunk. 10: Post. renal ganglion. 11: Aorticorenal ganglion. 12: Communication between suprarenal and renal plexuses. 13: Right coeliac ganglion. 14: R. phrenic nerve. 15: Post. vagal trunk and coeliac div. 16: Ant. vagal trunks. 17: Esophagus. 18: L. phrenic nerve. 19: Greater (thoracic) splanchnic nerve. 20: Lesser (thoracic) splanchnic nerve. 21: Lowest (thoracic) splanchnic nerve. 22: Sup. mesenteric ganglion. 23: Post. renal ganglion. 24: Intermesenteric nerves. 25: Renal branches from lower ends of intermesenteric nerves. 26: Lumbar sympathetic trunk. 27: L. ureter. 28: Inf. mesenteric plexus. 29: Sup. hypogastric plexus. [After Mitchell (211).]

NERVE SUPPLY TO THE KIDNEY: ANATOMICAL ASPECTS

Extrinsic Nerves

It is generally agreed that the major nerve supply to the kidney has its origin largely from the twelfth thoracic to the second lumbar ganglia of the sympathetic nervous system in man (51), and in the dog from T₄ through L₂, but most abundantly from T₁₀ through T₁₂ (31). Relative to its size, the kidney receives a more profuse and widespread supply than almost any other viscus. Mitchell (211) has written comprehensively on the anatomical aspects of the nerve supply to the human kidney, with an extensive historical review, and with good anatomical illustrations to which the reader is referred. Christensen *et al.* (55) have given a detailed description of the

innervation of the cat kidney. The renal nerves of the human kidney are derived from the following:

CELIAC PLEXUS. The renal branches arise from the celiac or aorticorenal ganglia, and contain sympathetic and almost certainly parasympathetic fibers. Most investigators feel that the posterior vagal trunk supplies the kidney via the celiac plexus, although several have indicated that it may pass directly to the renal plexus (fig. 13).

THORACIC SPLANCHNIC NERVE. The greater (superior thoracic) splanchnic nerve occasionally, and the lesser (middle thoracic) splanchnic nerve almost invariably send direct filaments to the aorticorenal ganglion or renal plexus, while the least (inferior thoracic) splanchnic nerve ends in the renal plexus.

LUMBAR SPLANCHNIC NERVES. Direct branches to the renal plexus may arise both from the first and second lumbar ganglia, or from the adjacent portions of the sympathetic trunk. These branches are inconsistent, especially the ones from the second lumbar ganglion. When present, they join the posterior root of the renal plexus often close to the terminations of the lowest splanchnic nerve, and sometimes they end in the posterior renal ganglia.

INTERMESENTERIC NERVES. The renal branches from the upper parts of the intermesenteric nerves run almost directly to the renal hilum. The uppermost ones are associated with those arising from the celiac plexus and occasionally from the superior mesenteric ganglion, and those a little lower down are connected with the origins of the superior spermatic nerves.

Other branches originate from the lower ends of the intermesenteric nerves or from the superior hypogastric plexus (presacral nerve). Except near their terminations they are separate from the other renal nerves; they communicate with the superior and middle spermatic nerves, and are apparently distributed mainly to the renal pelvis and upper ureter. Mitchell suggests that the ureter, renal pelvis, and renal collecting tubules may receive their parasympathetic supply via these nerves through the caudal (pelvic splanchnic) rather than cranial (vagal) outflow.

The various renal nerves unite in a plexiform manner around the renal artery. No filaments of any size lie anterior to the vein or posterior to the pelvis, and the plexus splits into subsidiary plexuses which accompany the branches of the renal artery into the kidney. A few filaments accompany the superior and inferior renal capsular veins. All nerves of the plexus do not cluster intimately around the renal artery, but several approach only the branches of this vessel in the actual hilum of the kidney. Both preganglionic and postganglionic nerve fibers exist in the renal plexus. The renal nerves and plexus form multiple intercommunications with many other autonomic nerves and plexuses.

Ganglia of varying size are invariably located in the plexus, and the posterior renal ganglion is the largest and most constant. Many of the ganglia are of microscopic size; these are more numerous in infantile kidney specimens, although not absent in adult kidneys.

Intrinsic Innervation

Mitchell (212) has emphasized the difficulties involved in the differential staining of intrinsic nerve

fibers; reticular fibers are especially troublesome and caution must be exercised in properly separating them from the nerves. Errors of interpretation have resulted from improper identification. The following description is largely from Mitchell and based upon the innervation in man.

The main renal plexus divides into large bundles which accompany the branches of the renal artery into the kidney, giving off interlobar, arcuate, and interlobular nerves corresponding to the divisions of the artery. They may lie adjacent to the arteries or be imbedded in the adventitia; some spread out in the adventitia and media, but others leave the vessels to run between the tubules. The nerve fibers in the adventitia do not all end in the artery, but may re-emerge into the perivascular space. Definite nerve filaments or endings were not found in the intima of any of the renal vessels, and no fine nerve plexuses were detected around the peritubular capillaries. The fibers are unmyelinated, according to Mitchell.

NERVE SUPPLY TO CORTEX. Nerve fibers are much more common in the cortex than in the medulla, and probably more frequent among the convoluted tubules. They are derived from the small bundles of nerve fibers associated with the interlobular arteries. At irregular intervals strands detach themselves from the parent bundles and pass between the tubules where they are connected by occasional anastomoses, and filaments may be traced to the limits of the cortex.

Many fibers appear to end as free, fine, beaded filaments on the basement membranes or between the tubular cells. Others give off short side branches which end in globular or fusiform swellings. Endings have been seen on the basement membranes and between the cells, but the presence of intracellular endings is doubtful. This aspect has been controversial: some workers believe that nerve fibers may end within the tubular cells (133, 161).

The glomeruli receive offshoots from the interlobular nerves and other filaments which are derived from adjacent interlobular nerve bundles. These offshoots run alongside afferent arterioles, and wind around them in a spiral fashion, supplying these vessels. Knoche (161) has demonstrated a terminal reticulum on the specialized cells of the juxtaglomerular apparatus (polkissen cell). Filaments proceed to the glomerulus, and Mitchell contends that the resultant strands fade away on the capsule or may end in a small series of slight varicosities. Dark staining strands (Romane's stain) have been seen within the glomeruli, but identification as nerves was

not absolutely positive. Knoche, on the other hand (using Bielschowsky-Gros stain), described a prominent terminal reticulum surrounding the glomerular capillaries. Since there are presumably no contractile elements of the smooth muscle type in the glomerular zone, the role of these nerve fibers becomes highly problematical. He also found nerve filaments around the efferent arterioles. Harman & Davies (133) saw nerve endings in the perivascular tissue of the glomerulus, and hypothesized an afferent function for them.

Knoche also described a prominent reticulum surrounding the complex made up of the macula densa, the polkissen, Goormaghtigh's "cell aggregate" and paravascular and paraportal cell clumps, and suggested that together they formed a receptor-effector zone to adjust glomerular filtration to the variations in blood pressure.

MEDULLARY NERVE SUPPLY. Comparatively few nerve fibers pass into the medulla as compared with the cortex, and most of these are located in the boundary zones. They reach the medulla largely through offshoots from the nerve bundles alongside the arcuate arteries, and by accompanying the arteriolae rectae spuriae. A point of control of the vasa recta system could reside here.

RENAL AFFERENTS. Beyond the possibility of presoreceptors in the field of the juxtaglomerular cell groups, the renal tissue is generally nonsensitive to afferent stimulation. Swelling gives renal pain via stretch of the capsule, which has pain afferents. It is said that some afferent sensory function is localized in the papillary tissue and in the pelvis.

DISTRIBUTION OF OSMOTIC CONSTITUTENTS IN THE KIDNEY; THE COUNTERCURRENT HYPOTHESIS

The osmotic constituents of the kidney are arranged so that they are isotonic with blood in the cortex, then rise to three to four times this concentration at the tip of the papilla. Wirz *et al.* (345) have demonstrated by a cryoscopic method (disappearance of ice crystals as observed by a polarizing microscope) that points of equal osmotic pressure form shells concentric to the tip of the papilla (fig. 14), and are parallel to the interzonal boundary. The important osmotic constituents are sodium, chloride, and urea, as revealed by the analysis of Ullrich & Jarausch (312) (figs. 15 and 16), and supported by the findings of Schmidt-Nielsen & O'Dell (267).

A uniform distribution of osmotic constituents

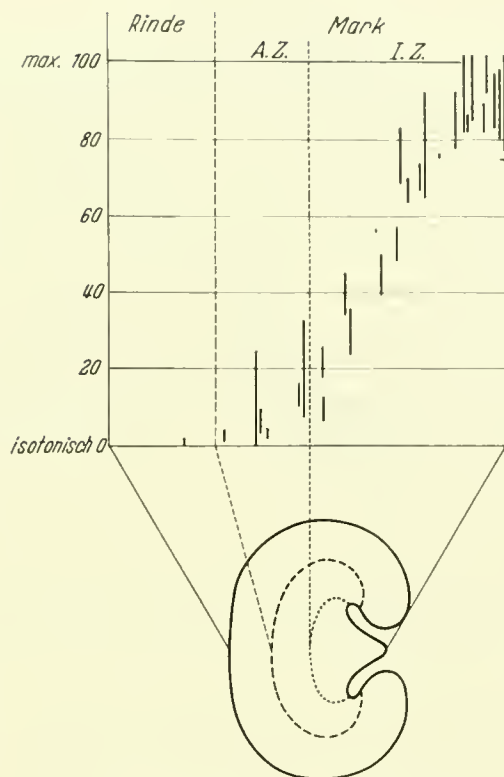


FIG. 14. Distribution of osmotic constituents in the kidney (hamster). A.Z.: outer zone of medulla; I.Z.: inner zone of medulla. [After Wirz *et al.* (345).]

between the loops of Henle, vasa recta, and collecting tubules has been proved by micropuncture (346, 348) in the hamster and rat (fig. 17) [Gottschalk & Mylle (113).] The "hairpin" loop arrangement of the loops of Henle and vasa recta has been the basis for the formulation of the countercurrent multiplier system concept for urinary concentration and dilution (132). (For discussion of this principle as applied to kidney function, see 131, 169, 171, 259, 289, 314.)

Briefly, the principle of the countercurrent system as it applies to the medullary loop of Henle system is as follows: sodium, by an active process, and chloride, as the result of an electrochemical gradient thus established, are believed to be transported out of the relatively water-impermeable ascending limb of the loop of Henle into the interstitium of the medulla until a gradient of ca. 200 mOsm per kg. H_2O has been established (fig. 17). This single effect is multiplied as the fluid of the thin part of the descending limb comes into osmotic equilibrium with the interstitial fluid by diffusion of water out (and probably by the diffusion of some NaCl into the descending limb), thus raising the osmolarity of the fluid rounding the hairpin loop into the ascending limb. The in-

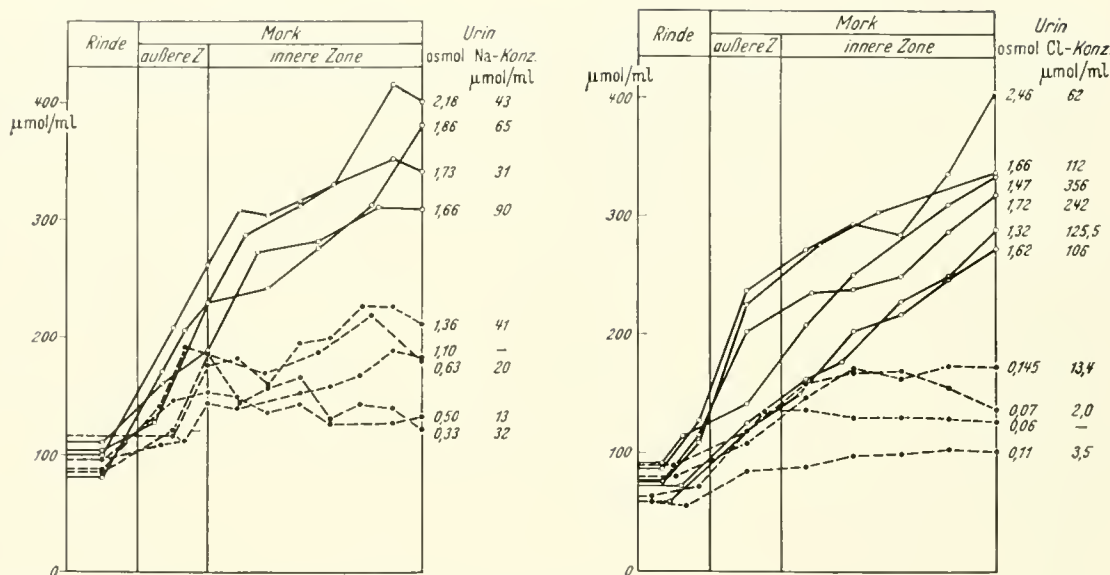


FIG. 15. Na and Cl concentration in kidney tissue ($\mu\text{mole/ml}$ of tissue fluid) in hydropenic (solid lines) and diuretic (dashed lines) dogs. To the right are the osmotic pressures, and Na and Cl concentrations of bladder urine taken shortly before the tissue analysis. [After Ullrich & Jarausch (312).]

creased concentration here, also raising that in the interstitium now favors further movement of fluid out of the descending limb, further increasing concentration, and so on.

In this fashion, an increasing osmotic gradient is established in the direction of the tip of the papilla, and yet at no level is there much osmotic difference among the luminal fluid, interstitial fluid, and blood. The collecting ducts in the presence of pituitary antidiuretic hormone (ADH) are believed to be water permeable and somewhat Na-impermeable (net transport small, although there may be diffusion into and active transport out). This results in diffusion of water out of the collecting ducts into the hyperosmotic medullary interstitium, and ultimately into the vasa recta to be carried away until fluid in the collecting ducts becomes correspondingly concentrated. The role of the vasa recta will be dealt with in greater detail below.

The view is currently favored that ADH acts in a permissive fashion to let water diffuse out of the nephron, perhaps altering the size of the "pores" in the base of the cells of the tubular epithelium. Figures 18 and 19 illustrate the operation of the countercurrent system in the concentrating and diluting kidney. In the concentrating kidney (fig. 18) ADH restores the hypotonic urine in the distal convoluted tubule to isotonicity by permissive (passive) loss of water and then permits its concentration to hypertonicity in the collecting duct. In the diluting

kidney, the distal convoluted tubule and collecting duct remain impermeable to water, and the urine remains hypotonic.

Mechanisms relating to salt and water handling in the proximal convoluted tubule, though highly important in a bulk sense, will not be dealt with here (see 279). Sodium is probably actively reabsorbed here, with water following passively.

RENAL BLOOD VOLUME; THE INTRARENAL HEMATOCRIT

The renal blood volume has been estimated in three ways: 1) by reconstructions of the vascular bed and from these estimation of the volume; 2) by the product of mean transit time of erythrocytes and plasma and the mean volume flow; and 3) by an injection of labeled erythrocytes (Cr^{51} , P^{32}) and labeled albumin (T-1824, I^{131}) with subsequent analysis of distribution in selected, homogenized tissue samples. Measurement of hemoglobin content has also served to assess erythrocyte volume.

By reconstruction techniques, Weaver *et al.* (332) computed the following distribution: 4.5 ml per 100 g of kidney in arteries, 4.1 ml per 100 g in cortical veins, and 2.6 ml per 100 g in subcortical veins, with about 2 ml per 100 g undetermined, distributed somehow among glomerular capillaries, efferent arterioles, peritubular capillaries, and medullary

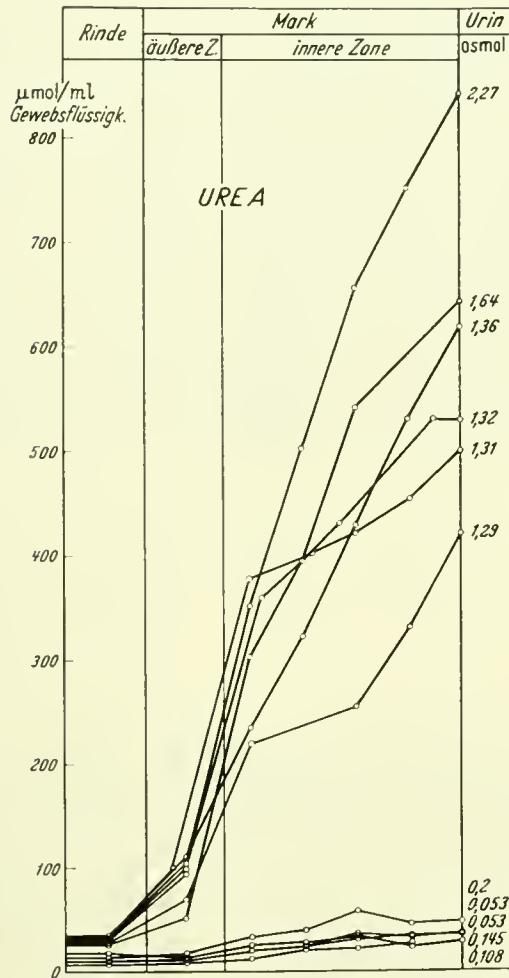


FIG. 16. Urea distribution in the dog kidney during hydropenia (upper curves) and diuresis (lower curves). [After Ullrich & Jarausch (312).]

vasculature for a total of 13.0 per 100 g of kidney. The interstitial fluid volume also averaged 13.0 ml per 100 g tissue (303). Hematocrit of kidney fluid drained from vein and artery was 27.0 per cent compared to the systemic hematocrit of ca. 43 per cent; this probably represented a combination of blood and "diluting" fluid (interstitial fluid). On the other hand, Morgan (219) placed a dog kidney, continuously pressured with blood from a carotid artery in a chamber filled with saline solution and intermittently stopped flow and expressed blood from the vessels (largely from the vein) by increasing the fluid pressure within the chamber. These samples showed hematocrit values only slightly lower than arterial blood. The expressed volume represented an average of 11.3 per cent of the kidney weight. Using Weaver's data for proportions, venous blood volume would be 54

per cent of the total. As to whether or not Morgan's samples contained more than venous blood would depend upon the figure accepted for renal blood volume. All injection methods yield values of 20 ml or more of blood per 100 g of kidney.

Computation of blood volume from the product of mean transit time and minute flow yields values of 20 to 24 ml per 100 g of kidney (66, 183, 185, 188) with a kidney hematocrit/large vessel hematocrit ratio of ca. 0.90. Transit time for red cells (\bar{t}_c) through the kidney is slightly faster than plasma (\bar{t}_p), e.g., $\bar{t}_c = 6.4$ and $\bar{t}_p = 7.6$ sec ($\bar{t}_c/\bar{t}_p = 0.83 \pm 5$) (183). The question as to whether this small difference in transit time supports the idea of red-cell shunting is debatable. However, Morgan (219) has advanced a cogent mathematical argument to show that a kidney/systemic hematocrit ratio as high as 0.83 could be enough to account for passage of significant amounts of cell-rich blood through shunting channels. Hemorrhage with lowered blood pressure did not influence the renal hematocrit (188) nor did KCN toxicity, which eliminates autoregulation of the flow (234). Hence the intrarenal hematocrit is not related to this phenomenon, a fact which argues against the cell-separation hypothesis of Pappenheimer & Kinter (240).

The third method tends to yield the largest volumes, averaging 27 ml per 100 g of kidney (84, 99, 182, 186, 240). The hematocrit ratio averages 20 per cent, slightly less than half of the systemic hematocrit ratio. It appears reasonable to assume that this method measures extravascular volume to a certain degree, accounting in the main for the difference from other methods. During the editing of this chapter a preliminary note has come to the author's attention (249a) in which it is claimed that washing out the renal vasculature yields a renal hematocrit part way between those given by the homogenate method and the mean transit time method.

The distribution of cells and plasma in various zones of the kidney appears in table 2 (186).

The findings of Emery *et al.* (84) are in essential agreement with the above with one exception: the papillary hematocrit is 47 per cent of the large vessel hematocrit; but this value is extremely variable in both groups of data, and may reflect the fact that this critical anatomical zone is supplied from two sources, the vasa recta and the spiral arteries.

Lilienfield *et al.* (184) point out that no significant difference in hematocrit exists between outer and inner cortex. This is interpreted as evidence against the cell-separation hypothesis for autoregulation of

FIG. 17. Distribution of osmotic constituents in tubules and vasa recta system of rats, indicating sites of active and passive sodium, urea, and water transport. The numbers represent hypothetical osmolarity values. No quantitative significance is to be attached to the number of arrows and only net movements are indicated. [After Gottschalk & Mylle (113).]

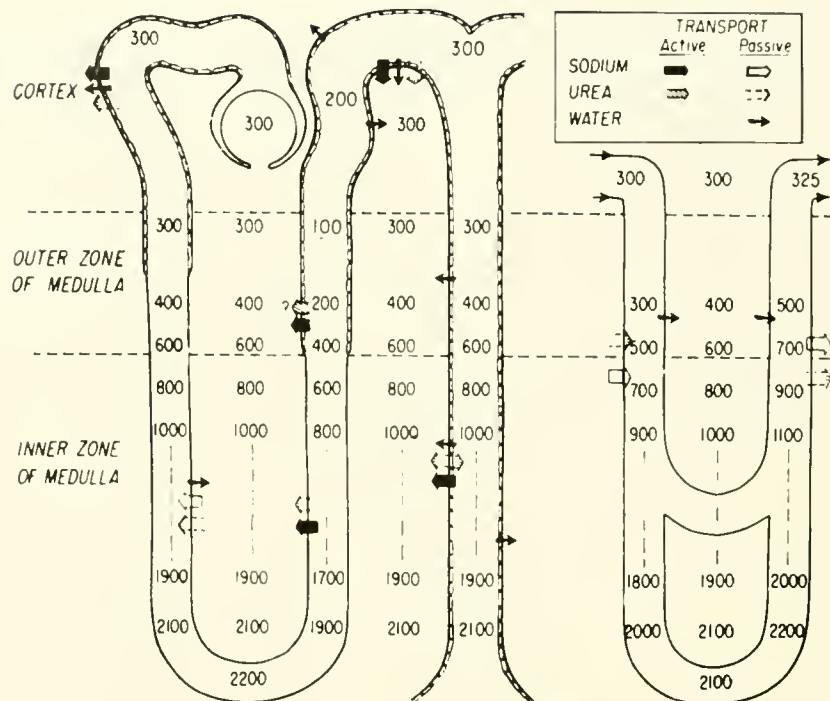
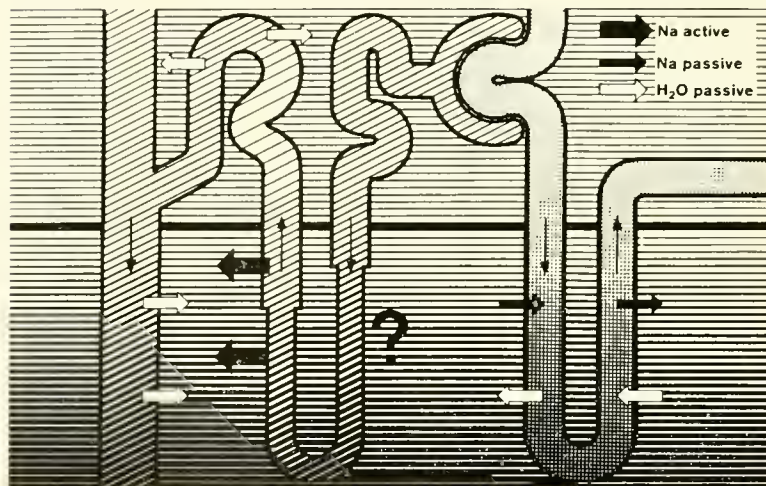


FIG. 18. Role of ADH in urine concentration and dilution in the countercurrent system. In the concentrating kidney, ADH acts in a permissive manner to facilitate water removal from the distal convoluted tubule and collecting tubule (white arrows) into the zone of hyperosmolarity. (Active sodium transport indicated by heavy black arrows.) Water and sodium exchanges in the vasa recta system are indicated as passive processes. The question mark at the descending limb of the loop of Henle indicates uncertainty as to the mechanism which initiates the countercurrent exchange. [After Wirz (349).]



renal blood flow (240), because plasma stripping in the interlobular arteries should lead to progressive hemoconcentration. The hemoglobin content of the cortical capillaries was found to be below that of the arterial blood hemoglobin, as measured by oximeter techniques (165). Emery *et al.* stoutly support the hypothesis by attributing the low hematocrit to axial streaming of cells in the many small vessels of the outer cortex. How this would fit into a concept of autoregulation by changes created in blood viscosity, and thus changes in vascular resistance (240), becomes difficult to envision. The somewhat higher

values in the inner cortex and outer medulla may reflect the hematocrit of larger vessels in this region.

Although Emery *et al.* believe that the low medullary hematocrit is further evidence of plasma stripping, it could be equally well explained by escape of labeled protein from the vasa recta into the interstitial spaces, a view supported by Swann *et al.* (303).

In dogs, autoradiographs appear to show a higher concentration of I^{131} -labeled albumin in the renal papilla than in other regions of the kidney (174). If a mechanism were to operate here to concentrate plasma albumin above normal levels, this could lead

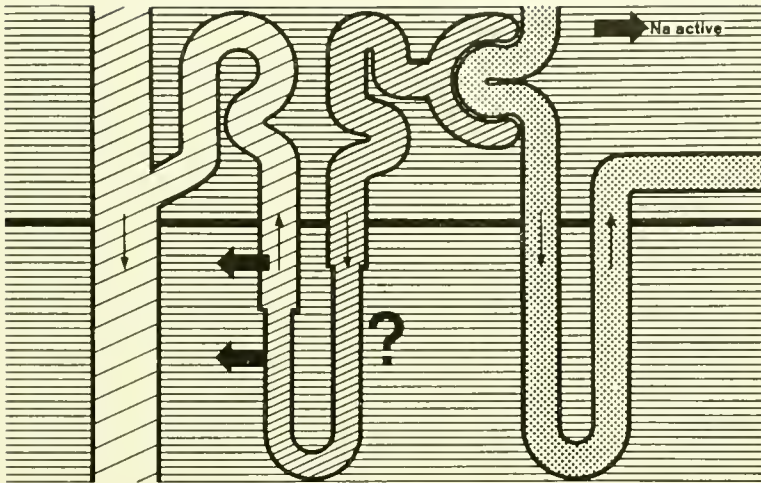


FIG. 19. The countercurrent mechanism during diuresis (absence of ADH action). [After Wirz (349).]

TABLE 2. Distribution of Cells and Plasma in Zones of the Kidney

| | | Outer Cortex | Inner Cortex | Outer Medulla | Inner Medulla | Outer Papilla | Inner Papilla | Whole Kidney |
|--------------------------|------|--------------|--------------|---------------|---------------|---------------|---------------|--------------|
| Cr ⁵¹ RBC | Mean | 5.5 | 6.9 | 10.4 | 6.3 | 3.6 | 3.5 | 7.2 |
| | S.E. | ±0.5 | ±0.7 | ±1.4 | ±0.8 | ±1.1 | ±1.0 | ±0.8 |
| I ¹³¹ Albumin | Mean | 22.8 | 24.0 | 30.7 | 34.6 | 37.0 | 38.5 | 25.6 |
| | S.E. | ±1.1 | ±1.2 | ±1.1 | ±2.2 | ±3.1 | ±2.5 | ±0.8 |
| Vascular vol. | | 28.3 | 30.9 | 41.1 | 40.9 | 40.6 | 42.0 | 32.8 |
| Tissue hematocrit | | 19.4 | 22.3 | 25.3 | 15.4 | 8.8 | 8.3 | 21.9 |
| Tissue hematocrit | | 43 | 50 | 56 | 34 | 20 | 18 | 49 |
| Arterial hematocrit | | | | | | | | |

All values as ml/100 g. [After Lilienfield *et al.* (186).]

to an erroneous impression of a larger volume of distribution for those substances which are bound by albumin. It is noteworthy that red cell volumes per gram of tissue are very similar in the medulla and the outer cortex (84), so that the low apparent hematocrit in the medulla is the result of the large "apparent" albumin space.

Confirmation of the high concentration of albumin in the loops of the vasa recta would lead to the interesting possibility of a countercurrent system for accumulation of albumin in the papillary portion of the loops. High concentration of albumin here would aid the rapid net transport of water from the interstitial space into the zone of elevated oncotic pressure, facilitating removal by the vascular system. The countercurrent exchange of water would begin at the juxtamedullary portion of the vasa recta by movement of water across to the ascending vasa rectae. The high interstitial content of protein, as

revealed by analysis of lymph (177) and the slow apparent flow of plasma through the vasa recta system [T-1824 transit time of 27.7 sec in the medulla as compared to 2.5 sec in the cortex (166)] are in support of this hypothesis.

Recently, strong evidence of a countercurrent system for water has been advanced by Morel *et al.* (218). They compared the kinetics of distribution of Na²² and tritiated water in the kidneys of oliguric hamsters. The concentration of the tracer in tissue samples removed at graded levels from cortex to papilla was measured. Na²² showed uniform distribution in less than 2 min, but the turnover of water in the deepest regions of the kidney was not complete in 10 min. This they attributed to the passage of water across the descending and ascending branches of the loops of Henle and vasa recta. Thus, the osmotic gradients of the hairpin system may supply the trigger

mechanism for the removal of water and concentration of albumin in the vasa recta loops.

METABOLIC ASPECTS

Oxygen Utilization

The renal venous blood contains considerably more oxygen than does venous blood from other tissues. The resulting small A-V oxygen difference [1.7 vol % in man (287), and ca. 3.0 vol % in the dog and cat] remains constant over a wide range of renal blood flows (66, 74, 102, 164, 180, 181, 317), although it may change at very low rates of flow. Thus, oxygen consumption (normally .08 to 0.10 ml g⁻¹ min⁻¹ in the dog) is related to flow, so that when flow is reduced as in shock (74) the organ ordinarily does not increase its extraction but apparently suffers curtailment of oxidative metabolism. As Pappenheimer & Kinter (240) have pointed out, the kidney behaves in a sense as a "flow-limited" tissue. The "cell-separation" theory proposed by them has attempted to reconcile the paradox of high renal venous oxygen saturation and flow limitation. If the majority of the red cells coursed through hypothetical shunts, then blood of low erythrocyte count, low in oxygen, would supply the tubular cells with a barely adequate supply of oxygen. If flow were impaired, oxygen supply would become insufficient, unless the blood flow could become redistributed to supply the tubular cells.

Levy (178) has brought evidence to bear against this hypothesis by showing that when additional oxygen was made available, the extraction of oxygen still remained constant over a wide range of blood flows, unattended by alteration of intrarenal hematocrit. In addition, 2,4-dinitrophenol was found to increase the renal oxygen extraction very significantly without altering the intrarenal hematocrit ratio. This implied that the capillary blood perfusing the renal tubules must not be virtually desaturated at normal or even at moderately reduced flows.

An alternative ingenious explanation was offered by Levy for the apparent flow limitation (179), based upon the earlier observation of Longley *et al.* (190). The latter showed that krypton⁸⁵ attained equilibrium very slowly between the circulatory system and the renal medulla. If these findings implied that krypton diffused from arterial to venous limbs of the medullary capillary circuits, it might be that oxygen would also diffuse across this path. Experimental verification appeared to be offered by the simultaneous injection

of highly oxygenated blood and blood containing methemoglobin-labeled red cells into the renal artery. Analysis of renal vein blood showed that the peak of elevated oxygen tension arrived slightly ahead of the labeled cells (1.25 ± 0.97 sec). Since the erythrocytes represent the portion of the blood that passes through the kidney most rapidly, it was concluded that some of the oxygen must diffuse from the vascular system and re-enter at some point downstream. The likely site for this operation is between the upper arterial and venous limbs of the vasa recta. In support of this is the fact that oxygen pressure of the renal venous blood is always higher than that of the urine (253). This could be explained by supposing that urine in the collecting tubules tends to equilibrate with blood of low oxygen tension in the vasa recta before entering the pelvis.

The implication of this is that the medullary zone of the kidney and particularly the region of the papilla would be a zone of decreased oxygen tension compared to the cortex. The low hematocrit here would further compromise the oxygen supply (84, 166, 184). Lastly, volume flow in the medulla has been measured by an ingenious intrarenal photoelectric technique and found to be small, 21.8 ml per min per 100 g compared to 400 ml per min per 100 g in the cortex (166).

But the operation of the countercurrent system does not demand increased oxygen utilization by the cells of the medulla. Ullrich (314) has summarized the result of a number of Warburg tissue-slice studies made in the guinea pig, dog, and cat. The average values are as follows in cubic millimeter per milligram of dry tissue per hour: cortex, 21.3; outer medulla, 15.1; inner medulla, 6.2. A representative experiment made on guinea pig kidney tissue by Grupp & Hierholzer (115) appears in figure 20.

These findings would support the conclusion that the important structures of the inner medulla (loops of Henle and collecting ducts) do not have important energy requiring functions. Ullrich & Pehling (313) have shown that tissue slices of the outer medulla of the dog kidney increased their oxygen uptake as a linear function of NaCl concentration in the bath. While oxygen uptake of the outer medulla was stimulated by addition of 200 μ M NaCl per ml, this produced only a slight depression of oxygen uptake by slices from the cortex and inner medulla. It is the outer medullary zone that contains the portion of the ascending thick limb of the loop of Henle where the active sodium pump appears to be located, based on the puncture studies. However, evidence of active

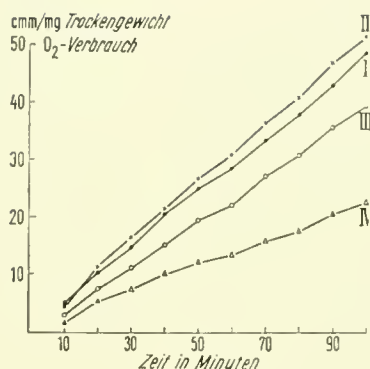
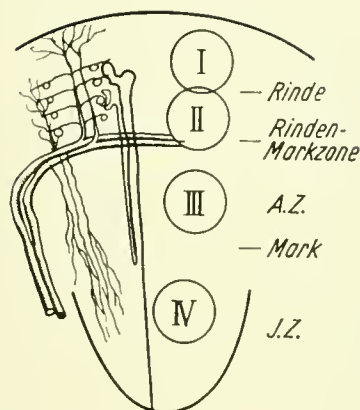


FIG. 20. Oxygen utilization (mm^3/mg tissue dry weight) in various zones of the guinea pig kidney. [After Grupp & Hierholzer (115).]

sodium reabsorption in the collecting tubules has been recently adduced by microcatheterization (140). This process probably involves an ion-exchange mechanism with K and NH_4 akin to that operating in the distal convoluted tubule (315).

Heat Production

Grupp *et al.* (116, 117) have calculated that a dog kidney of average weight of 40 g and an average surface of 6.0 cm^2 produces ca. 8 cal per min (0.18 cal/g/min). Fregler (95) found an average of $0.52 \text{ cal per g per min}$ ($0.29\text{--}0.78$). By insertion of small thermistor probes to varying depths into the dog kidney, Ochwaldt & Schmier (232) and Grupp & Janssen (117) were able to compare the temperature difference at varying depths from the surface of the kidney to the renal arterial blood. The distribution of the temperature gradient appears in figure 21. Note the highest values in the cortex, a drop at the cortico-medullary junction, and a secondary increase in the medulla. Since differential flow effects could complicate the picture, heat production was measured by Janssen & Grupp (151) in kidneys in which the circulation was stopped for 1 to 3 min. In these, the cortex averaged 0.162°C above arterial blood, and in the medulla, 0.113°C , confirming the above trend.

The higher heat production in the cortex is related to its higher metabolism. The dip in the gradient at the corticomedullary junction could be explained by the more direct influence of the large vessels lying in this zone, reflecting systemic temperature. The temperature gradient correlates only roughly with that of oxygen utilization. If flow in the medulla is indeed as slow as the measurement of Kramer *et al.* (166) would indicate, heat storage could be a factor in the relatively higher temperature in the medulla.

Grupp & Janssen (117) have related the heat

turnover of the kidney to the blood flow by the formula: turnover (per sec) = $K \cdot F [(\theta_R - \theta_A)/(\theta_V - \theta_A)]$, where F is the flow (ml/min); K is a constant based on the timing and the specific heat of kidney tissue and blood; θ_R is the temperature within the renal tissue; θ_A is the temperature in the renal artery; and θ_V is the temperature in the renal vein.

The mean trend is shown in figure 22. Above a flow of 2 ml per g per min, the turnover is directly related to flow. Below this value, turnover slows noticeably and becomes quite independent of flow. Environmental factors (conduction, etc) must now have a greater effect than flow on heat removal.

PRESSURE GRADIENTS IN THE RENAL VASCULAR CIRCUIT

Pressure Gradient

Ideal circumstances for analysis of pressure gradients in the renal vascular circuit would require direct micropuncture of representative segments of the vessels. The only mammal in which this has been done for analysis of pressure is the rat (112, 347), and then only in the peritubular capillaries of the cortical tubules. Coupled with this were measurements of intratubular (proximal) pressure. The results appear in table 3. Wirz (347) reported data from 17 anesthetized male rats which were in excellent agreement: in proximal tubules, 14.8 mm Hg (to 22); in 5 of these animals, postglomerular capillary pressure was $17.4 \pm 2.6 \text{ mm Hg}$. Using Winton's (343) estimate that glomerular pressure is 65 per cent of arterial pressure, the following gradient probably exists in the rat: mean arterial pressure, 100 mm Hg ; glomerular capillary, 65 mm Hg ; peritubular capillary pressure, 16 mm Hg ; and renal vein pressure, 2.0 mm Hg (111).

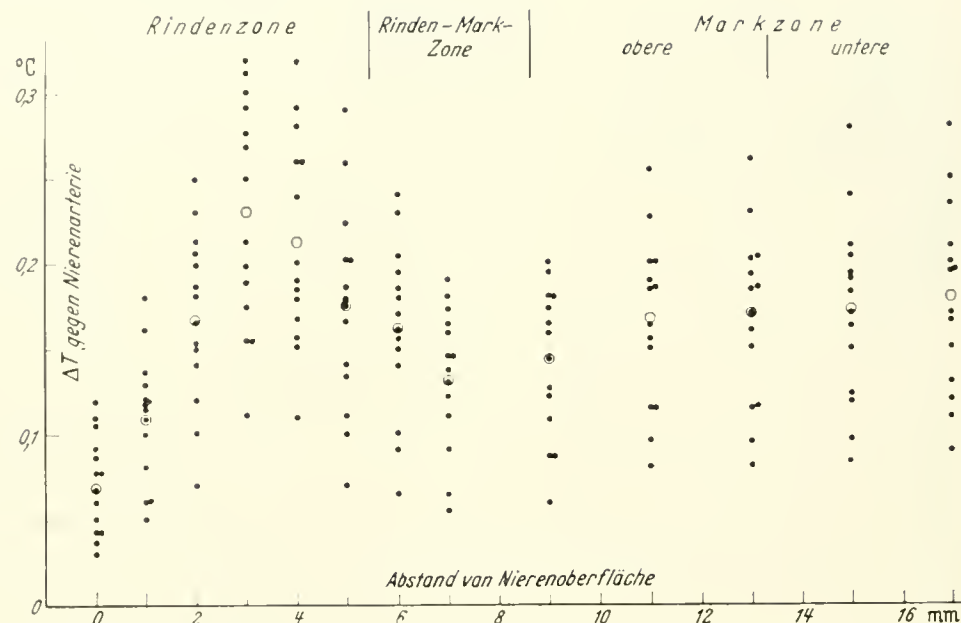


FIG. 21. Zonary temperature gradients in the dog kidney (ordinate: ΔT compared to arterial blood; abscissa: depth from kidney surface in mm). Rindenzone: cortical zone; Rinde-Markzone: juxta-medullary zone; obere Markzone: upper medullary zone; untere Markzone: deep medullary zone. [After Janssen & Grupp (151).]

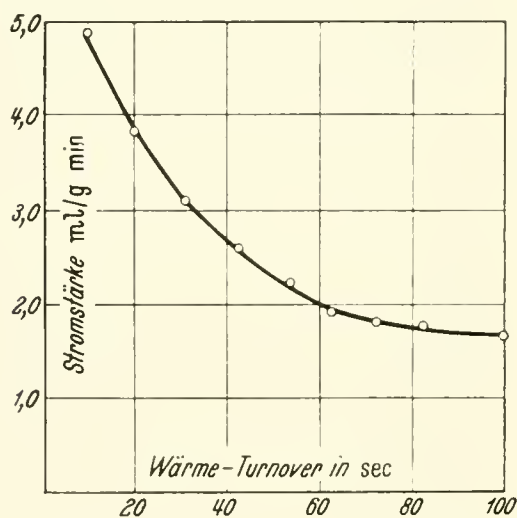


FIG. 22. Heat turnover in sec (abscissa) related to renal blood flow in ml/g/min (ordinate). [After Grupp & Janssen (117).]

Swann (342) has postulated, based in part on estimates and in part on direct measurement of intrarenal, arcuate vein, and renal vein pressure, the hydrostatic pressures which probably exist in the dog kidney. The estimates appear in figure 23. The relatively high capillary pressures, compared to that of the rat, may be due to the higher intrarenal pressure recorded in the dog, 16 to 26 mm Hg, compared to an average of 10 mm Hg in the rat.

Critical Closure; Yield Pressure

The term "critical closing pressure" (CCP) was introduced by Burton (46) in his analysis of the physical factors controlling the equilibrium of small blood vessels. Critical closing pressure is defined as the arterial pressure in a local vascular bed at which flow through the area becomes zero. When flow is plotted against pressure, there is a positive intercept on the pressure axis when flow is zero. It has been suggested that CCP is dependent on vasomotor tone, and hence can be used as an index of this tone. Its relation to intrarenal tissue pressures becomes of interest in connection with the latter's role in the phenomenon of autoregulation of renal blood flow.

Measurements of the so-called CCP for the kidney have been made in cats by Yamada & Åström (4, 352), and in dogs by Hinshaw *et al.* (141). The technique involves perfusion of the in situ or isolated organ by pump or from a reservoir at steady pressures. Arterial and venous pressure are measured with optical manometers or electromanometers. Venous outflow is recorded. The decay gradients of pressure and flow are recorded during brief occlusion for an arbitrary period lasting 2 to 2.5 min as employed by Yamada and Åström or until pressures have plateaued (Hinshaw *et al.*) and flow has stopped. At the end of this time, arterial (P_{Ar}) and venous

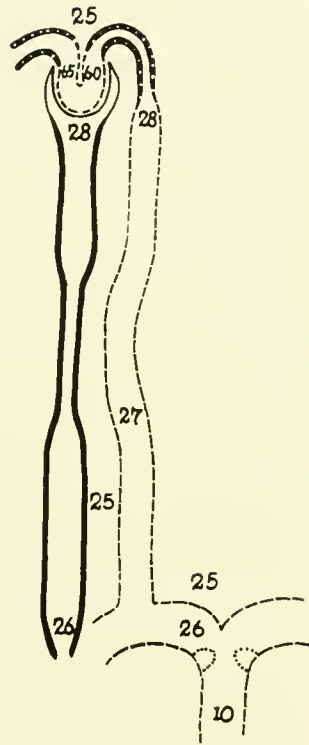


FIG. 23. Estimates of hydrostatic pressures (mm Hg) in the dog rephron and associated vasculature [After Swann (342, discussion).]

(P_{V_f}) pressures are measured, and the A-V difference calculated.

In 15 experiments on the kidney (nerves intact) (352), P_{A_f} averaged 12.0 ± 4.1 (SD) mm Hg, and P_{V_f} , 5.0 ± 2.9 . The $P_{A_f} - P_{V_f}$ difference was 7.0 ± 3.6 mm Hg. Another series (4) agreed very closely. The minimum arterial pressure for flow (P_{A_f}), in this situation corresponding to critical closing pressure, was of the same order of magnitude as the "yield pressure" in the dog (7–14 mm Hg) (120, 258, 271, 282).

Arterial pressure flow (P_{A_f}) (preferred to CCP because of the probability of inherently different connotation) and $P_{A_f} - P_{V_f}$ can be experimentally varied under a variety of circumstances. The values

TABLE 3. Relation Between Intratubular and Peritubular Capillary Pressure in Unmanipulated Kidneys

| Pressure Measured | No. of Rats | Avg. of Measured Values, mm Hg | Avg. of Adjusted Values*, mm Hg |
|------------------------|-------------|--------------------------------|---------------------------------|
| Intratubular | 21 | 13.8 | 13.8 |
| Small capillary | 11 | 14.2 | 14.0 |
| Large capillary | 8 | 20.4 | 18.7 |
| Unclassified capillary | 7 | 16.7 | 15.4 |

* Adjusted for rat differences by the statistical technique of disproportionate subclass numbers in the analysis of variance. [After Gottschalk & Mylle (112).]

are lowered by nerve section and ganglionic blocking agents. They are increased during the reflex response to carotid occlusion and noradrenaline intra-arterial injections and to cooling (352).

The role of tissue pressure is of importance, particularly as influenced by the renal venous pressure and the possibility of a venous-arteriolar reflex. It was found that when pressure-time curves were determined at venous pressures of 15 to 60 mm Hg (4), that P_{A_f} and P_{V_f} became identical in 8 of 12 cases, and in the remaining 4 ranged from 2 to 6 mm higher than venous pressure (P_V) at the end of 2 to 2.5 min of occlusion.

The P_{A_f} at elevated venous pressure was never greater than the sum of the control P_{A_f} and the applied venous pressure, implying a lack of increase in vasomotor tone as the result of increasing venous pressure, and arguing against a venous-arteriolar reflex.

Identical pressure at the elevated venous pressure implies that the distensible resistance vessels have increased their caliber or in some manner permitted the pressure to equilibrate. In the four cases with consistently higher P_{A_f} an explanation of "prevailing high vasomotor tone alone or in combination with an initially high intrarenal pressure" was offered. In any event, Åström believes that the interstitial pressure in the kidney is more important than the vasomotor tone as a determinant of the P_{A_f} and the $P_{A_f} - P_{V_f}$ difference.

Hinshaw *et al.* (141) related the apparent CCP to tissue pressure changes in dog kidneys. Stabilized values following clamp of inflow and after cessation of flow were 1.7 mm Hg, for $P_A - P_V$ pressure difference, and 2.9 mm Hg for tissue pressure. The correspondence of values led them to the conclusion that the A-V pressure differences were the result of the tissue pressure; the somewhat higher value for the tissue pressure indicated incomplete transmission of pressure across the walls of the vessels. At any rate, the manifest CCP could be accounted for by the tissue pressure, they believed. If so, then the active vasomotor tone would be negligible in the kidney under these experimental conditions. This conclusion held for kidneys in situ (nerves intact) as well as their pump-lung-kidney preparations.

The conclusion reached by Åström was that CCP in the kidney in the sense employed by Burton need not be assumed and that the P_{A_f} more appropriately should be considered as a yield pressure, that pressure needed to start flow against the compressing effect of the interstitial pressure. It should be added here that the term "yield pressure" as originally employed

for the kidney circulation by Selkurt (271) connoted an element of the viscous properties of the blood looked upon as a fluid manifesting plastic flow.

Intrarenal Pressure

Such pressures have been obtained, with minor variations in technique among various investigators, by insertion of small-gauge needles (no. 24-27) into the renal substance to varying depths, introduction of small volumes of saline (0.1-1.0 mm³) through the needle tip, and reading the stabilized pressure with low volume-displacement manometers. What this pressure represents is debatable and probably cannot be interpreted as interstitial pressure in the classical sense. De Langen (71) has reviewed the vagaries of renal interstitial pressure measurement. The small pool of fluid immediately surrounding the tip of the needle probably represents pressure from damaged blood vessels, tubules, glomeruli, and lymphatics. Since it best reflects changes in venous pressure, it would appear that these vessels are the usual sites of entry. Swann *et al.* (302) have shown that intrarenal pressure and arcuate vein pressure are equal (coefficient of correlation 0.85) in a range of intrarenal pressures of 6 to 73 mm Hg.

Although in the strictest sense this should perhaps only be called "needle" pressure, a designation preferred by Winton (343), Gottschalk (111, 112) has chosen to call it interstitial pressure. Others have designated it as "intrarenal pressure" (IRP), a term preferred here in the belief that it reflects directly or indirectly renal interstitial pressure as a part of the integrated pressure which is recorded by the needle-puncture technique. Renal interstitial pressure has been considered to be the resultant of a number of component factors: *a*) intravascular pressure and volume, *b*) glomerular filtrate and urine volume, *c*) external renal capsule elasticity, *d*) Bowman's capsule volume and elasticity, and *e*) stroma rigidity.

Winton (340-342) has employed an indirect method to measure intrarenal pressure, which he has defined as a pressure exerted in all directions throughout the substance of the organ, tending to obliterate collapsi-

ble structures such as peripheral parts of tubules and venules. In isolated dog kidneys, intrarenal pressure was taken to approximate ureteral pressure when the latter was elevated to a degree which caused a decrease in urine flow.

Needle pressures for the dog kidney are summarized in table 4.

Gottschalk found the IRP somewhat lower in smaller animals (rats, guinea pigs, rabbits, and cats), averaging 10 mm Hg (4-19) in 65 animals, a value equal to that found in dogs by Winton when he employed his indirect method (340).

FACTORS WHICH MODIFY INTRARENAL PRESSURE. *Relation between venous pressure and IRP.* When venous pressure was raised by graded compression of the renal vein in 12 rats, rabbits, and dogs, the IRP was not affected until venous pressure approached the pre-existing intrarenal pressure, which then began to rise (111). At renal venous pressures above 20 mm Hg, IRP followed venous pressure very closely and was at most 1 or 2 mm Hg more than venous pressure through a range exceeding 100 mm Hg. The results of Swann *et al.* (300) in the dog were very comparable, except that IRP started at a higher control value (25 mm Hg).

Relation of ureteral pressure and intrarenal pressure. Increased ureteral pressure probably increases IRP by compressing the intrarenal veins (111). In 12 rabbits and dogs elevating the ureteral pressure to 15 and 30 mm Hg raised the IRP from a control average of 10 mm Hg to averages of 14 and 19 mm Hg, respectively. Elevating ureteral pressure to 50 mm Hg increased IRP from a control value of 8 to 21 mm Hg in 11 rabbits and from 12 to 27 mm Hg in 4 dogs. Ureteral pressure is about half as effective as venous pressure in elevating IRP.

Arterial pressure influence on intrarenal pressure. Results of different investigators are quite discordant. Winton (341) in a range of 80 to 100 mm Hg found no consistent change in IRP by the indirect method. The other workers used needle punctures. Gottschalk (111) observed no effect until mean arterial pressure was reduced below 40 mm Hg, when IRP fell abruptly. Miles & DeWardener (206) found that as mean arterial pressure was decreased from 120 to 20 mm Hg in dogs by clamping the aorta, IRP fell from 27 to 10 mm Hg. Hinshaw *et al.* (143-145) also found IRP varied with arterial pressure in the zone of autoregulation. Swann *et al.* (301) found the best correlation; a plot of IRP against arterial pressure exhibited a coefficient of correlation of 0.85, and

TABLE 4. *Intrarenal Pressure (mm Hg) in Dog Kidney*

| | Mean | Range | No. of Animals |
|--------------------------------|------|-------|----------------|
| Montgomery <i>et al.</i> (215) | 26 | 10-58 | 42 |
| Swann <i>et al.</i> (300) | 25 | 10-59 | 11 |
| Gottschalk (111) | 16 | 12-25 | 8 |
| Miles & DeWardener (206) | 21 | 8-35 | 15 |
| Winton (343) | 21 | 11-45 | 23 |

showed that IRP was related to mean arterial pressure (\bar{P}_A) as follows: $IRP = 9.4 + .22 \bar{P}_A$. Thus, when arterial pressure increased 1 mm Hg, IRP increased 0.22 mm Hg.

Other factors: a) *location of needle tip.* Gottschalk compared needle pressure in the cortex versus the medulla. In rats and rabbits there was no significant difference. In dogs, repeated determinations were more variable, but there were no consistent differences in deep and superficial measurements. Winton (343) has recorded a much higher IRP in the medulla than in the cortex (fig. 24). This may have particular significance in interpretation of the countercurrent system (vide infra).

b) *Decapsulation.* Miles & DeWardener (206) found no difference in IRP as the result of decapsulation. Nor did differences appear as IRP was increased by osmotic diuresis (mannitol), elevation of venous pressure, and increase in perfusion pressure after KCN elimination of renal circulatory autonomy. Winton and Swann reported a reduction of IRP to about one-half as the result of decapsulation (342). Although the latter results seem most logical, the former investigators emphasize the necessity of care in handling to avoid decreases in IRP due to vasoconstriction, and the need for an adequate recovery period before measurements are made. The significance of the change of IRP with decapsulation will be considered further below in relation to the problem of renal circulatory autonomy.

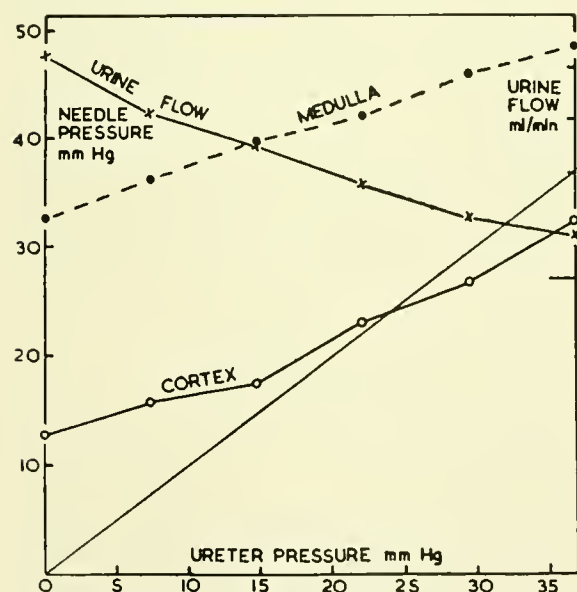


FIG. 24. Needle pressures in medulla and cortex of the dog kidney related to ureter pressure. The straight diagonal line represents perfect correlation. [After Winton (343).]

Intrarenal pressure and the countercurrent system. Reduction in urine volume and electrolyte output of the kidney as the result of increase in venous and ureteral pressure are well-known phenomena (127, 273, 277, 279). Increases in intrarenal pressure could favor reduction in urine volume in several ways: pressure on the collecting ducts would slow movement of urine in this segment and favor removal of water molecules to the zone of hyperosmolarity, operationally dominated by ADH. Secondly, compression of the vasa recta would slow the flow of blood and favor uptake of water into the hyperoncotic zone. Finally, a high interstitial pressure could favor inward flow. If the observation of Winton (fig. 24) that IRP is higher in the medulla than in the cortex can be confirmed, particularly specific and effective mechanism would exist.

The mechanism underlying decreased excretion of electrolytes is more complex, involving among other factors alterations in load offered to the tubules resulting from changes in filtration rate brought about by venous and ureteral pressure elevation (127, 273, 277, 279).

MEASUREMENT OF RENAL BLOOD FLOW

Methods

Both direct and indirect methods have been employed. Direct methods employ flowmeters of various types which record either arterial inflow or venous outflow. These include the following: thermostrohmuhr or direct-recording strohmuhr (Ludwig type); rotameter; bubble flowmeter; electromagnetic flowmeter; direct venous outflow (cylinder and stopwatch). The indirect methods are an application of the renal clearance principle. This is based on the clearance (C) ratio: $C = \frac{U}{P} V$, in which U is the urinary concentration in mg per ml, V is the minute urine volume, and P is the plasma concentration (usually systemic vein) in mg per ml. [For methodology, including the use of clearance techniques, see (272, 288).]

The plasma clearance of inulin (C_{In}) has been universally proved to be solely by glomerular filtration. In dog and other mammals (except anthropoids) the clearance of creatinine (C_{Cr}) is also a measure of filtration rate.

The requisite for the clearance of a substance to measure plasma flow is that it be entirely removed (or nearly so) from the plasma in one transit through

the kidney. This is verified by examination of the concentration in the renal vein (V_c). Such can be related to the renal arterial plasma concentration (A_c) as the extraction ratio E : $E = (A_c - V_c)/A_c$. Hence, if $V_c = 0$, E will equal 1.0. E is less than unity to the extent that the material is not removed by urinary excretion. It is clear that if the clearance is divided by the extraction ratio (C/E), the resultant quotient will yield the total renal plasma flow (RPF).

$$RPF = \frac{\frac{UV}{P}}{\frac{A_c - V_c}{A_c}}$$

This formula is an expression of the Fick principle, for if P be taken as A_c (systemic venous plasma concentration equal to renal arterial plasma concentration), we have:

$$RPF = \frac{\frac{UV}{A_c}}{\frac{A_c - V_c}{A_c}} = \frac{UV}{A_c - V_c}$$

In order to obtain total renal blood flow, the hematocrit measurement of the blood is introduced:

$$RBF = \frac{C}{E(1-\text{hemat.})} \text{ or } \frac{UV}{(A_c - V_c)(1-\text{hemat.})}$$

Several substances are so efficiently removed by combined processes of glomerular filtration and active tubular (proximal) transport (secretion) at low plasma concentrations, that the renal vein concentration is very low (i.e., extraction nearly complete, and E close to unity). These include Diodrast (D) and *p*-aminohippurate (PAH) (287, 288). Then C_D or C_{PAH} is nearly equivalent to plasma flow. The fact that extraction is not complete is interpreted as indicating that a small fraction of blood does not perfuse excretory tissue: this would include capsule and inert supportive tissue, medullary tissue (loops of Henle, collecting ducts), calycine mucosa, and pelvis. On this basis, Smith has referred to this as the "effective" plasma or blood flow.

A considerable amount of study has been made of the extraction ratios of Diodrast and PAH. A representative group of findings is shown in table 5.

Although E_D and E_{PAH} seem comparable in the dog, E_{PAH} is more efficient in man than E_D . This was particularly the experience of Bergstrom *et al.* (16) who made simultaneous comparisons ($E_{PAH} = 0.90$; $E_D = 0.74$). Differences in kinetics of erythrocyte to plasma shift for PAH may be involved, and this is

TABLE 5. Renal Extraction of Diodrast and PAH

| Investigators | Animal | Mean | Range |
|-------------------------------|--------|------|-----------|
| <i>I. Diodrast</i> | | | |
| White (338) | Dog | 0.74 | 0.61-0.85 |
| Corcoran <i>et al.</i> (59) | Dog | 0.84 | 0.79-0.96 |
| Hemingway & Schweitzer (137) | Dog | 0.73 | 0.62-0.87 |
| Study & Shipley (298) | Dog | 0.74 | 0.66-0.81 |
| Kinter & Pappenheimer (160) | Cat | 0.73 | 0.63-0.92 |
| Josephson <i>et al.</i> (152) | Man | 0.73 | 0.70-0.79 |
| Bergstrom <i>et al.</i> (16) | Man | 0.74 | 0.58-0.86 |
| <i>II. PAH</i> | | | |
| Selkurt (269) | Dog | 0.74 | 0.64-0.94 |
| Phillips <i>et al.</i> (247) | Dog | 0.87 | 0.83-0.91 |
| Thompson <i>et al.</i> (305) | Dog | 0.75 | 0.51-0.90 |
| Ascheim <i>et al.</i> (3) | Dog | 0.82 | 0.75-0.90 |
| Kinter & Pappenheimer (160) | Cat | 0.85 | 0.78-0.93 |
| Warren <i>et al.</i> (327) | Man | 0.90 | 0.85-1.00 |
| Bradley & Bradley (32) | Man | 0.93 | 0.90-0.94 |
| Cargill (49) | Man | 0.90 | 0.83-0.93 |
| Maxwell <i>et al.</i> (198) | Man | 0.92 | 0.88-0.97 |
| Josephson <i>et al.</i> (153) | Man | 0.89 | 0.85-0.92 |
| Bergstrom <i>et al.</i> (16) | Man | 0.90 | 0.88-0.93 |

probably less important for man than the dog. A factor to be considered is that the animal work has done largely under anesthesia, while the human subjects were unanesthetized.

The Fick principle can be employed with any substance cleared by the kidney which shows a measurable A-V difference. Obviously, the smaller the A-V difference, the more prone to error the calculation will be. Thus, phenol red, urea, mannitol, and inulin have been employed, but have considerably smaller A-V differences than Diodrast and PAH.

THE NITROUS OXIDE METHOD. This is an adaptation of the method employed for the measurement of cerebral blood flow and involves inhalation by the subject of nitrous oxide, and uptake from the blood by the kidney. The Fick principle is employed (58, 68).

$$RBF_{N_2O} = \frac{100V_{c,t'} \cdot S}{\int_0^{t'} (A_c - V_c) dt}$$

RBF_{N_2O} is the blood flow per 100 g kidney tissue per minute as measured by N_2O uptake; $V_{c,t'} \cdot S$ is the kidney uptake of N_2O per g tissue during the time from 0 to t' (time of blood-tissue equilibrium); and A_c and V_c are arterial and renal venous concentrations, respectively, which finally become equal at time t' . S is the partition coefficient between blood and tissue (assumed to be unity in this instance).

The method yields an average of 3.2 ml per min per g kidney weight in anesthetized dogs (58) and in man (68). Comparison of this method with a direct method (bubble flowmeter) in the dog under various physiological conditions shows that the two yield flow values which are not significantly different (58). An obvious advantage is that the nitrous oxide method can be employed during conditions of anuria. A similar application using radioactive krypton (Kr^{85}) has been employed during anuria (40).

Critique of the Clearance Method

CRITERIA FOR APPLICATION OF CLEARANCE. Some of the criteria which must be met in order for the clearance of a substance such as Diodrast or PAH to measure accurately renal plasma flow are: *a*) change of volume of blood in passage is negligible (i.e., urine and lymph flow not excessive), *b*) concentration of substance in blood is constant, or the rate of change of concentration is uniform for midpoint collection, *c*) rate of urine flow should be sufficiently large and constant so that it may be representative of the urine in the nephrons, *d*) the substance should not be formed or altered in the kidney, *e*) all blood in the renal vein should pass through the kidney (and not enter via shunts).

FACTORS WHICH MIGHT INVALIDATE THE CLEARANCE METHOD. *a*) Oliguria or marked fluctuations in urine flow such as might accompany rapid changes in blood pressure. If there is stagnation, or rapid fluctuation of the urine flow in the nephrons, the collected sample will not reflect the true excretion, and the midpoint plasma sample will lack validity. *b*) Rapid changes in plasma concentration, preventing establishment of equilibrium among blood, interstitial fluid, tubular cells, and tubular urine. *c*) Renal storage of substance in tubular cells or interstitial fluid. *d*) Storage of substance in the erythrocytes in excess of the plasma concentration, so that its simple outward diffusion through the plasma adds appreciably to the amount actually carried by the plasma leading to an erroneous plasma flow figure. *e*) Impairment of the PAH tubular transfer mechanism, leading to an erroneously low plasma flow figure.

ADEQUACY OF C_D AND C_{PAH} AS MEASUREMENT OF RENAL PLASMA FLOW. Under stabilized conditions that fulfill the criteria explained previously, good correspondence of clearance to direct methods is obtained. Selkurt (269) found that BF_{PAH} averaged 91 per cent

of the simultaneously measured direct blood flow (venous outflow method). The difference was attributable to incomplete extraction of PAH. Conn & Markley (57) compared renal blood flow in anesthetized dogs as measured indirectly by the Fick principle (PAH clearance) to blood flow measured directly by bubble flowmeter. The ratio of indirect to direct values averaged 1.025. Employment of the Fick principle corrects for incomplete extraction and yields total blood flow. Schwalb *et al.* (268) made a similar comparison and found a ratio of 1.06 ± 0.17 . But after the kidney was poisoned with Na fluoride, the agreement did not hold. Then flow measured by the bubble flowmeter was often much higher than that measured by PAH clearance. Since the use of the Fick method should correct for incomplete extraction due to impairment of the PAH secretory mechanism, the authors believed that PAH was stored in the kidney (possibly in the tubular cells) so that excretion (UI) was low, relative to the apparent removal.

Reubi *et al.* (255) compared simultaneous Fick plasma flows for PAH, mannitol, endogenous creatinine, and thiosulfate. For example, the ratio between C_{PAH}/E_{PAH} and C_M/E_M varied between 1.54 and 0.645. Disparities were further exaggerated by injection of epinephrine and histamine causing rapid transients in blood pressure and urine flow. Suggested causes for the discrepancies were: differences in the extraction and blood flow in separate kidneys; intrarenal extraction; conjugation or breakdown of PAH, mannitol, creatinine, and thiosulfate; removal of part of the substances from the kidney through lymphatic vessels, thus bypassing the renal vein; changes in the permeability of the red cells to the test substances; or, finally analytical difficulties. Bálint & Fekete (8) found great disparities between direct blood flow and the Fick method (C_{PAH}/E_{PAH}) in hemorrhagic hypotension, hemorrhagic shock, and shock from pyloric obstruction in dogs. The indirect method was always lower by varying degrees than the direct method.

Since errors are compounded by the analysis of Reubi *et al.*, it would be more desirable to compare the indirect methods against a direct method in tests for fidelity under experimental conditions. Under circumstances of rapidly changing blood flow resulting from nerve stimulation or action of vasoactive drugs, as has been suggested, the clearance method may not accurately follow direct flow. Study & Shipley (298) found excellent agreement between the Fick method (Diodrast) and direct flow (rotameter in renal vein) during control conditions. During stimulation of the

renal nerves, resulting in a 53 per cent reduction in direct flow, the calculated RBF was from 1 to 70 per cent of the true values because of reduction in urine flow and incomplete excretion (U^*). All calculated flows exceeded the direct flows on cessation of stimulation as stored urine was washed out. They emphasized the need to correct for possible shifts of Diodrast (or PAH) from erythrocytes to plasma during the venous sampling. To the extent that this occurs, the E_D or E_{PAH} will be vitiated, and the Fick application inaccurate. Phillips *et al.* (247) have given methods for correction of PAH shift. Whole blood extraction eliminates errors incurred by the shift from cells to plasma, and Bergstrom *et al.* (16) have found the use of radioactive Diodrast (containing I^{131}) particularly helpful in this respect. The possibility has been examined that opening of vascular shunts not perfusing excretory tissue might occur following nerve stimulation or drug action and invalidate the clearances. Epinephrine (0.1 μ g) in rabbits caused the E_{PAH} to fall to negative values in seven of nine cases [average for the seven, -26.6% (214)]. This was restored in 10 to 40 min. The negative values have been explained by a return to the venous outflow of stored PAH (interstitial fluid of papillary zone?). Injections of Thorotrast in these pictured the possibility of juxtamedullary shunting of blood. Ephedrine produced a similar picture in cats [India ink injection (189)], but Löfgren points out that the picture of cortical ischemia and medullary filling could result from congestion of the vasa recta following contraction of venous effluent constrictors, rather than from opening of a bypass and increased flow. Moyer *et al.* (222) employed sciatic stimulation and epinephrine in dogs and rabbits. With sciatic stimulation, blood flow decreased ca. 36 per cent, but renal venous blood never became arterialized, as the original Trueta shunt operation would demand. In fact, the A-V oxygen difference actually increased. India ink distributed fairly equally throughout cortex and medulla after nerve stimulation. The rabbit kidney after epinephrine, however, appeared to confirm the appearance of cortical ischemia and subcortical injection. But the latter does not necessarily mean increased medullary flow. Epinephrine and histamine caused a maximum decrease of E_{PAH} of only 11.4 per cent in the human kidney (254).

In an interesting experiment Cargill (48) infused human serum albumin into patients. E_{PAH} invariably decreased significantly, even as C_{PAH} increased. C_{In} rose proportionally to C_{PAH} , so that the filtered

fraction remained constant. These results could readily be explained by increased shunting of blood through the medullary vasa recta system.

EXTRACTION RATIO AS A TEST OF VALIDITY OF THE CLEARANCE METHOD. The extraction ratio has been one of the measurements which yields insight into the efficacy of the tubular transfer process or the adequacy of tubular vascular perfusion. It is reduced during shunting of blood away from the tubular secretory sites, or as the result of actual impairment of the transport mechanism. Some of the physiological and pathological conditions in which renal extraction has been evaluated follow.

E_{PAH} is not reduced by abdominal compression which elevates control venous pressure from ca. 6 mm Hg to 18 mm Hg (32). This lack of effect on E_{PAH} may be due to the probability that transmural renal venous pressure would not be changed by this maneuver (329). Werkö *et al.* (334) found no change in E_{PAH} during the renal ischemia induced by tilting. E_{PAH} may be normal or only slightly impaired in essential hypertension. A series examined by Reubi & Schroeder (254) averaged 0.84, including one of 69.8. Cargill's (49) series of hypertensive patients including those with nephrosclerosis averaged 0.79 (0.58–0.91). The lowered values are associated with reduction of C_{PAH} below 300 ml per min. In anemia, there is only a slight decrease of the ratio (256, 305). In nine observations on subjects with no renal pathology but in congestive heart failure, Merrill (202) found only two below 0.85 (0.64, 0.63); Edelman *et al.* (78) reported an average of 0.90 (0.88–0.91) in ten congestive heart failure subjects.

In nephritis there may be considerable reduction in the extraction ratio. Bradley *et al.* (33) obtained values for E_{PAH} ranging from 0.58 to 0.76 in six subjects with chronic glomerulonephritis. It may be supposed that in the course of disorganization of the renal vascular pattern, channels are established in which blood flows from the artery to vein without exposure to functional tubular tissue (abnormal shunts or destroyed excretory tissue). Marked reduction in E_{PAH} (as low as 0.034 and 0.106) was noted with tubular damage resulting from carbon tetrachloride poisoning (284). E_{PAH} decreased during acidemia which developed during the apnea of diffusion respiration in dogs (27). The control E_{PAH} of 0.86 at pH 7.4 decreased to 0.53 at 7.05.

Renal ischemia and anoxic damage resulting from hemorrhagic shock will impair extraction. Twenty

minutes of renal ischemia in dogs resulted in a reduction in E_{PAH} from 0.74 to 0.59 (269). Control flow (C_{PAH}) which gave 91 per cent of the simultaneous direct blood flow measurement decreased to 30 per cent of the direct flow as a consequence of ischemia. Recovery occurred in 85 min. After 2 hours of ischemia (246), E_{PAH} (control, 0.90–0.94) was reduced to 0.11 to 0.43.

Phillips *et al.* (247) found adequate extraction of PAH until renal plasma flow was reduced below 7 ml per min during hemorrhagic hypotension and then clearances no longer reflected plasma flow accurately. Corcoran & Page (62) stated that C_{In} did not have value as a measure of plasma flow during severe, prolonged hypotension, nor immediately after restoration of blood pressure by transfusion. Diodrast clearance fell progressively on repeated hemorrhage and transfusion, until in some instances negative extraction values were obtained (as low as -1.59 compared to control of 0.757). On transfusion, an "over-shooting" of clearances beyond the control was observed during the early stages as a result of washing out of material accumulated in the interstitial fluid and stagnant urine during hypotension. Selkurt (270) compared C_{PAH} with a direct blood flow method in dogs during hemorrhagic hypotension and shock. *p*-Aminohippurate clearance virtually ceased during hypotension (60–40 mm Hg) as direct flow fell to 11 per cent of control. On transfusion, although direct flow was rapidly restored to near control, blood flow calculated from C_{PAH} averaged only 39 per cent of direct flow, as the result of anoxic tubular impairment. E_{PAH} during hypotension was low and variable with numerous negative extraction values (range, -0.750 to 0.543 during a 90 min period at 60 mm Hg, and -1.50 –0.285 during 45 min at 40 mm Hg). After transfusion, E_{PAH} partially recovered, averaging 0.406 (0.03–0.69) compared to the control of 0.73. Clearly the hypotensive anoxia had invalidated the C_{PAH} clearance as a measure of plasma flow probably because of consequent tubular damage.

The negative extraction during hypotension has been explained as the result either of back diffusion of PAH from the lumina of damaged nephrons into venous blood (270), or of absorption into the renal venous blood of PAH accumulated during the period of hypotension and impaired urinary excretion (62). Again, this may be PAH concentrated in the vasa recta and interstitial fluid in proximity (counter-current mechanism), and will thus imply continued,

TABLE 6. *Clearance Data in Mammals and Renal Blood Flow in Dog*

| | Per g KW ml/min | | Per kg Body Wt ml/min | | Per 1.73 m ² BSA ml/min | |
|--------------------------------------|--------------------|-----------|--------------------------|-----------|---------------------------------------|-----------|
| | C_{In} | C_{PAH} | C_{In} | C_{PAH} | C_{In} | C_{PAH} |
| <i>A. Clearance Data in Mammals*</i> | | | | | | |
| Rat | 0.75 | 2.75 | 6.00 | 22.0 | 70 | 253 |
| Rabbit | 0.66 | 2.50 | 3.12 | 18.2 | 87 | 512 |
| Dog | 0.62 | 1.91 | 4.29 | 13.5 | 146 | 460 |
| Man | 0.46 | 2.33 | 1.97 | 10.0 | 118 | 600 |
| <i>B. Renal Blood Flow in Dog†</i> | | | | | | |
| | RPF | RBF | RPF | RBF | RPF | RBF |
| Unanesthetized‡ | 2.08 | 3.80 | 12.5 | 22.7 | 463 | 845 |
| Anesthetized§ | 1.89 | 3.40 | 13.0 | 23.4 | | |

KW = kidney weight, BSA = body surface area.
 * [From Smith (287).] † (From *Handbook of Circulation*, WADC Tech. Rpt. 59-593, 1959.) ‡ 220 Observations; direct venous outflow; urea, phenol red, and PAH extraction. § 58 observations; (pentobarbital and chloralose); direct venous outflow, rotameter, and bubble flowmeter.

but reduced, perfusion of the medullary zone, with cortical ischemia.

Renal Blood Flow Values

Data have been culled from two important sources in the summary presented in table 6. It will be noted that the dog appears to have the lowest C_{PAH} per gram kidney weight. The rat's value for C_{PAH} is least per 1.73 m² body surface area, increasing progressively in the series to the value in man. The dog has the highest filtration rate (C_{In}) relative to the effective plasma flow (C_{PAH}), giving a filtration fraction (FF) of 0.32. In man this is 0.20.

In summary, as Smith has repeatedly stressed, the clearance methods yield adequate information on renal hemodynamics only under conditions of relative stability of flow. They cannot accurately follow rapid changes of blood flow, and changes in pathological states (e.g., shock kidney) seriously handicap their utility.

EXTRINSIC REGULATION OF RENAL BLOOD FLOW

Neurogenic Control

The thoracolumbar sympathetic supply is a rich source of vasoconstrictor fibers for the kidneys. The

vagus apparently contains no vasomotor fibers to the kidney, and no evidence exists for vasodilator fibers in this circuit. Hence, the vasomotor status of the kidney is maintained by variations in vasoconstrictor tone.

THE QUESTION OF RENAL AUTONOMY. Considerable controversy has revolved around the question of whether or not a continued flow of impulses passes to the arterioles, or whether such regulation is absent in the basal state, to be invoked only in emergency states of heightened sympathetic nervous system activity. Early investigators, working in anesthetized animals, appeared to demonstrate a "denervation hyperemia." In view of the fact that ample evidence exists that morphine, ether, chloroform, urethane, and pentobarbital anesthesia depress renal blood flow to varying degrees, probably due to enhanced activity of the sympathetic system and adrenal medulla, it is understandable that removal of the neurogenic source of renal vasoconstrictor activity would result in a relative hyperemia, e.g., with unilateral denervation. Earlier work in this area has been reviewed by Smith (287) and Carstensen & Holle (51).

When clearance techniques are employed in trained, unanesthetized dogs, which have recovered well from the effects of surgical denervation of one kidney, or denervation and transplantation of one organ, function is equal in the experimental and control kidneys. This includes concordance of glomerular filtration rate (creatinine or inulin clearance), plasma flow (Diodrast or PAH clearance), and indeed, diuretic activity and electrolyte excretion (17, 35, 139, 197, 257, 299).

Carstensen & Holle (51) performed sympathectomies at the levels of the first and second lumbar vertebrae (L₁ and L₂) in patients suffering with arteriosclerotic obliterans and endarteritis obliterans. Clearances of phenolsulfonphthalein (PSP), creatinine, and PAH were measured before and after the operation. Although individual results were quite variable, the average changes were not significant: endogenous creatinine clearance for glomerular filtration rate (GFR), 127 ± 42 before; 136 ± 59 , after; PAH clearance, 340 ± 67 before; 366 ± 92 after. Unilateral sympathectomy (from T₈ to L₁, and greater and lesser splanchnics) in patients with essential hypertension did not increase blood flow on the operated side (104), and both kidneys responded by an equal reduction in flow after Adrenalin administration.

Smith *et al.* (285) demonstrated in normal, un-

operated human subjects that spinal anesthesia up to T₅ or higher did not produce renal hyperemia as measured by the Diodrast clearance, nor did it have any other consistent effect on the renal circulation. They concluded that the renal blood flow is normally determined by autonomous, intrinsic activity of the renal arterioles and is not dependent upon the tonic activity in the sympathetic pathways, which show continued action potentials (263).

It must be emphasized that despite its inherent autonomy of circulation, the kidney will respond with vasoconstriction during enhanced activity resulting from direct electrical stimulation of the renal nerves in the dog, rabbit, cat, and rat (81, 148, 167, 222, 298, 319); this is reversed by a variety of sympatholytic drugs (81, 319). Studies of blood distribution in the rabbit kidney supplemented with India ink injection techniques, revealed that the resulting ischemia was largely cortical, and that the blood supply to the medullary zones was not noticeably altered (25). Houck (148) examined the effect of electrical stimulation of the renal nerves of anesthetized dogs on blood flow (PAH clearance), filtration rate (creatinine clearance), and T_m (tubular maximum) of PAH and glucose (G). By relating filtration rate to unit of tubular excretory tissue (filtration/T_m_{PAH}), and reabsorptive tissue (filtration/T_m_G), and the perfusion of active tubules with blood (RBF/T_m_{PAH}), it was discerned that regions of ischemia were produced, with random closure of nephrons. This was verified by the distribution of India ink injected into the renal artery. The evidence was that the effects resulted predominantly from constriction of the afferent arterioles. Blood was not shunted from the cortex to the medulla. Study & Shipley (298) also believe the effects are largely on the afferent arterioles. They too found no evidence of shunting.

Strong afferent stimulation (acute tracheal compression, sudden clamping of an upper or lower extremity, and sciatic nerve stimulation (25, 65, 66)) likewise caused renal vasoconstriction on a reflex basis. Pain caused by intense cold stimulation of the hand, or pressure headaches, resulted in decreased clearance of Diodrast and of inulin to a lesser degree (filtration fraction increased), while blood pressure increased (351).

More subtle reflex mechanisms have been discerned. Bladder distention in chloralosed cats gave reflex increases in blood pressure; apparently the kidney participated in the vasoconstriction as manifested by decreases in volume (229). Bilateral splanchnectomy abolished the viscerovascular response.

An ureterorenal reflex was described by Hix (146). When a catheter distended the ureter in the dog, ipsilateral plasma flow and GFR decreased. The afferent stimulus facilitated further decrease in these functions during emotional stimulus. Anesthetization of the ureter or surgical denervation abolished the reflex. The physiological significance of such viscerovascular reflexes is not apparent; but it can be suggested that the circumstances evoking the reflex (bladder distention, ureteral irritation) are such that cessation of urine production would be beneficial, at least temporarily.

CENTRAL NERVOUS SYSTEM (CNS) CONTROL OF RENAL BLOOD FLOW. Evidence exists that a representation of control of the renal circulation exists in the cerebral cortex. Smith (286) in 1940 presented an example of psychogenic renal vasoconstriction, as evidenced by a marked decrease in the Diodrast clearance; the inulin clearance decreased only slightly, so that FF increased. Meehan recently has confirmed the observation that emotional states will cause a decrease in renal plasma flow (PAH clearance) (200). Cort (66) observed reduction of A-V oxygen and carbon dioxide differences in the cat kidney during stimulation of the supraorbital cortex, signifying reduction in flow. Hoff *et al.* (147) acutely stimulated two cortical foci in cats on the right and left anterior sigmoid gyri, or applied more diffuse chronic stimuli to the rostral surface of the cranium. Ischemia of the renal cortex (revealed by India ink injection) resulted, with little effect on the renal medulla. When denervated, the kidney was passively engorged as the blood pressure rose. Chronic stimulation for a number of days led to tubular degeneration as a result of the continued ischemia.

Wise & Ganong (350) stimulated the hypothalamus, pons, and medulla oblongata of pentobarbitalized dogs with chronically implanted electrodes. Effects on glomerular filtration, and excretion of water and electrolytes were studied. Influence on GFR was variable: stimulation of the dorsal medulla just lateral to the midline led to a rise in blood pressure with an associated decline in GFR and urine volume, abolished by renal denervation. Stimulation of an area in the obex, in and near the area postrema, led to a rise in GFR and urine volume, without significant change in blood pressure. Other points stimulated in the brain stem (medulla, pons, midbrain, and posterior hypothalamus) had no effects on GFR and electrolyte excretion, even though some stimuli caused changes in blood pressure.

Thus, the CNS control of the renal circulation is intimately wrapped up in the general problems of higher regulation of the cardiovascular system. As these become worked out, better insight into renal control will eventuate (241).

Humoral Control; Pharmacologic Agents

ADRENERGIC. *l*-Epinephrine and arterenol (levarterenol, norepinephrine) are both active vasoconstrictors of the renal vasculature. The comparative potency, and the site of action is not entirely settled, depending upon technique employed, e.g., indirect clearance techniques with intravenous injection, or direct flow studies with intra-arterial injection. The latter method, employed by Spencer *et al.* (292) has an obvious advantage in that local effects can be observed without demonstrable alteration of systemic pressure. Flow measurement was made with an electromagnetic flowmeter in dogs. Table 7 shows the effect of the same dosage of epinephrine and arterenol as measured by the volume of blood shunted from the kidney. Only at a 10 μ g dose is the difference significant, and at this dose epinephrine appears to be the more effective.

Werkö *et al.* (335) compared the effects on clearances (C_{in} and C_{PAH}) done in man. The substances were given in approximately the same dosage during two experimental periods, following control. An attempt to assess the differential site of action was made by application of the formula of Gómez (105) for calculation of regional vascular resistance. The average values appear in table 8.

As Spencer *et al.* found, the differences between the action of these two adrenergic drugs are not great, and here arterenol appears to be the more effective. For both, the greatest degree of resistance change was in the afferent arterioles. Maxwell *et al.* (199) injected 1.0 to 1.5 mg of epinephrine intramuscularly in human subjects, and noted a decrease of 13 per cent

TABLE 7. *Effect of Epinephrine and Arterenol on Renal Blood Flow in the Dog*

| Dose, μ g | No. of Paired Observations | Avg. ml of Blood Shunted by: | | Mean Difference <i>l</i> -Epinephrine Arterenol | | |
|------------------|----------------------------------|---------------------------------|-----------|----------------------------------------------------|------|-------|
| | | Epinephrine | Arterenol | Avg. | SE | P |
| 1 | 9 | 58.5 | 33.8 | 24.5 | 21.2 | 0.3 |
| 3 | 9 | 69.8 | 58.4 | 11.3 | 10.6 | 0.36 |
| 10 | 10 | 217.0 | 148.7 | 68.3 | 18.4 | 0.005 |

[After Spencer *et al.* (292).]

TABLE 8. *Comparative Effects of Epinephrine and Arterenol on Human Renal Vascular Dynamics*

| Procedure | C_{In} | RPF | FF | \bar{P}_A | Vascular Resistance in Dynes·sec·cm ⁻⁵ | | | |
|-------------------------|----------|-----|------|-------------|---------------------------------------------------|-------------------|-------------------|-------------------|
| | | | | | RAa | RAe | RV | Total resistance |
| | | | | | × 10 ³ | × 10 ³ | × 10 ³ | × 10 ³ |
| Control | 115 | 665 | 0.18 | 100 | 2.71 | 1.60 | 2.89 | 7.19 |
| Arterenol 20.4 µg/min | 111 | 498 | 0.22 | 121 | 5.42 | 2.13 | 3.73 | 11.27 |
| Control | 128 | 660 | 0.19 | 100 | 2.53 | 1.92 | 2.88 | 7.33 |
| Epinephrine 24.5 µg/min | 129 | 553 | 0.23 | 113 | 4.04 | 2.29 | 3.54 | 9.85 |

[After Werkö *et al.* (335).]

in C_{In} and 40 per cent in RPF; FF increased by 39 per cent. Also employing Gómez' calculation, they computed that the greatest resistance increase was in the venular and venous component, and suggested that this contributed significantly to the kidney volume increase that had been noted some time ago from epinephrine, the so-called "paradoxical expansion" of Richards and Plant. The work of Mehrizi and Hamilton (201) in the dog kidney has confirmed this conclusion for arterenol. Note that in the data of Werkö *et al.* (table 8), RAe (efferent arteriolar resistance) and RV (venous resistance) increased equally after epinephrine, and the change was most pronounced in RAa (afferent arteriolar resistance).

Studies were made in which measurements of Tm_G and Tm_{PAH} were combined in the dog and human (149, 208). In the dog, the ratio GFR/Tm_G decreased significantly, due to over-all reduction in filtration rate in each glomerulus, rather than nephron shutdown, according to Houck (149). But Mills *et al.* (208) state that GFR and Tm_G decrease together with epinephrine and arterenol, implying nephron closure; this might be anticipated with higher dosage. In the human, the dosage employed (0.243 µg/kg min of epinephrine, 0.321 µg/kg min of arterenol) caused no significant alteration of GFR or Tm_{PAH} , although RBF fell to 63 per cent of control. Changes in E_{PAH} were never observed by several groups of workers.

SYMPATHOMIMETIC DRUGS. Several sympathomimetic substances have been studied for comparative effects on renal blood flow (5, 114, 293). None of a series of rapidly acting vasodepressors, such as isoproterenol and ethylarterenol, injected into the renal artery of dogs (flow measured by electromagnetic flowmeter) induced vasoconstriction (114, 293). Epinephrine, tried in this series, caused the most potent constriction. The amylbutyl and isobutylamine derivatives of arterenol, even in quite large doses, were devoid of any renal vasomotor action despite the fact that they

exhibited definite vasodepressor actions on the systemic circulation. It was concluded that the renal circulation does not exhibit sympathetic inhibitory receptors.

Aviado *et al.* (5) grouped a number of drugs into four categories, based upon effects observed in the dog kidney by intrarenal arterial or systemic intravenous injection. Direct flow was measured by rotameter. *Type A:* Drugs which are capable of constricting renal vessels when injected into the renal artery or when given intravenously: levarterenol, epinephrine, phenylephrine, metaraminol, methoxamine, and nephazoline. *Type B:* Drugs which constrict when injected into the renal artery but, when injected intravenously, constriction is not always encountered: ephedrine, phenylpropanolamine, hydroxyamphetamine, and compound 45-50. *Type C:* These have no important actions when injected into the artery. When injected intravenously, renal blood flow is increased because of their systemic pressor effect: methamphetamine, pseudoephedrine, amphetamine, pholedrine, methylaminoheptane, tuaminoheptane, mephentermine, and phenylpropylmethylamine. *Type D:* Drugs that have a local dilator action; when they are injected intravenously, renal blood flow is decreased as a result of arterial depressor action: isoproterenol, nylidrin, isoprophephamine, methoxyphenamine, and cyclopentamine. Spencer (293) reported a weak constrictor action by isoproterenol, but this was not encountered in the above series because smaller doses were used.

A similar analysis of various sympathomimetic drugs on renal hemodynamics has been made recently by Mills *et al.* (210), employing clearance in normotensive and hypotensive drugs. In this series, mephentermine had the least effect on GFR and RBF, and methoxamine the greatest.

GANGLIONIC BLOCKING AGENTS. Ganglion-blocking drugs interfere with the reflex adjustments of the circulation. They block the vasoconstrictor pathways

which control peripheral resistance and venous return and hence prevent the rise in blood pressure which results from such maneuvers as clamping the carotids, cutting the pressoreceptor nerves, the Valsalva maneuver, and the cold pressor test. Essentially, they eliminate efferent nervous influences which keep blood pressure up. The fall in blood pressure which results from their administration may, in part, be due to decrease in cardiac output. Peripheral vasodilatation and increased flow may occur, e.g., in the limbs, in the presence of a fall in blood pressure, or at least in the absence of a rise. There appears to be little or no direct effect on the vasculature. Responses of the splanchnic organs, including the kidney, may be quite different: decreased blood pressure is accompanied by decrease in flow.

Hexamethonium chloride. Moyer *et al.* (225) gave 2 to 5 mg per kg (iv) and observed an average drop of 138 to 97 mm Hg in the blood pressure in 20 dogs anesthetized with pentobarbital or chloralose. Glomerular filtration rate showed no change (46–45 ml/min), RPF decreased from 182 to 172 ml per min, and FF varied from 0.26 to 0.28. Renal vascular resistance (RVR) decreased from 0.57 to 0.48, and Tm_G showed little alteration (161–155 mg/min).

In patients (220), with a greater fall in blood pressure at the dosage used, blood pressure fell to 66 per cent of control. C_{In} decreased to 78 per cent, and C_{PAH} was maintained at 98 per cent of control, signifying decrease in RVR. One must consider the possibility that renal autonomy may account for this, rather than dilatation due to drug action. In another series, in normotensive and hypertensive patients (209), blood pressure decreased to 80 to 85 per cent of control following dosage of 5 to 75 mg. In half no change or actual increase in RVR occurred, so that GFR and RPF were reduced at the time of maximum decrease of blood pressure. In the other half, RVR decreased so that GFR and RPF were maintained despite the fall in blood pressure. There was no effect on E_{PAH} .

Arfonad (trimethaphan camphorsulfonate) has a greater depressing effect on renal function (GFR and RPF) than hexamethonium, due to greater reduction of blood pressure (227); RVR is not significantly altered in normals. In patients with nephrosclerosis (243) C_{PAH} , originally reduced, tended to be maintained despite a fall in blood pressure to 40 to 50 per cent of control; C_{In} was noticeably reduced. The intensity of renal vasoconstriction in dogs, produced by clamping the aorta or limb trauma, was relieved by Arfonad blockade (26).

Other blocking agents. Pendiomid (azamethonium

chloride), administered to patients with no vascular disease at the rate of 2 to 6 mg per min for several hours (avg 250 mg over 3 hours), caused blood pressure to fall from 97 to 71 mm Hg. Renal blood flow decreased in about the proportion of the decline in blood pressure, with no significant change in RVR (228). Ecolid (chlorisondamine) in hypertensives shows maintained renal blood flow despite significant fall in blood pressure (77). Tetraethylammonium bromide is a renal vasoconstrictor, according to Aas & Blegen (1) as revealed by the more marked fall in C_{PAH} than systemic pressure. Priscoline (tolazoline), state Young *et al.* (353), is a vasodepressor and a renal constrictor both in humans and dogs. Marked decrement in GFR occurs, along with somewhat lesser decrease in RPF, and they believe the major site of action is on the afferent arterioles. After denervation of the kidney, Priscoline has no effect, and Young and his group suggest that the drug causes afferent arteriolar stimulation via the sympathetic innervation. Ilidar (azapetine) directly injected into the renal artery has no effect up to a dose of 3 mg; above this, it is a constrictor (292). Regitine (phentolamine) is both vasodepressor and vasodilator in dogs (226) at infusion rates of 3 mg/kg for over 5 min RBF increased from 307 to 341 ml per min, despite a decline in blood pressure from 134 to 102 mm Hg. Dibenzylamine (phenoxybenzamine) was injected into one renal artery of the dog, followed by infusion of arterenol systemically. Marked decrease in GFR and RPF occurred in the untreated kidney, but not in the treated kidney (129). Dibenzylamine (N,n'-dibenzyl-B-chloroethylamine hydrochloride) caused definite remission of enhanced vasomotor tone resulting from hemorrhage in dog (34), but did not alter the outcome of hemorrhagic shock.

OTHER VASOACTIVE DRUGS. *Apresoline* (hydralazine) is a vasodepressor which reduces vascular resistance in the kidney. It is not a ganglionic blocker, but its exact mechanism of action is unknown, although it has been suggested that it may antagonize neurohumoral substances (such as serotonin, pherantoin, and angiotensin) which are believed to affect blood pressure. Table 9 shows its effects in normal subjects and acute nephritics (dosage, 0.2–2.5 mg/kg, orally).

While improving normal blood flow, Apresoline unaccountably increased vascular resistance of the nephritics, despite a fall in systemic pressure. That hypertension per se was not basic to this response is shown by the effects in essential hypertensives studied by Gjörup & Hilden (101). While mean blood pres-

TABLE 9. *Effect of Apresoline on Renal Hemodynamics in Normal and Nephritic Humans*

| | GFR | RPF | RBF | FF | PA | RVR |
|------------------|-----|-----|------|------|-----|-------|
| <i>Normal</i> | | | | | | |
| Before | 135 | 560 | 872 | .244 | 92 | 0.108 |
| After | 111 | 665 | 1116 | .173 | 74 | 0.067 |
| <i>Nephritic</i> | | | | | | |
| Before | 95 | 594 | 928 | .164 | 126 | 0.150 |
| After | 60 | 456 | 717 | .120 | 99 | 0.197 |

[After Etteldorf *et al.* (86).]TABLE 10. *Effects of Serotonin on Renal Hemodynamics in the Unanesthetized Dog*

| Dose $\mu\text{g/kg/min}$ | GFR ml/min | | Urine Vol. ml/min | | RPF ml/min | | P |
|------------------------------|---------------|-------|----------------------|-------|---------------|-------|-------|
| | Before | After | Before | After | Before | After | |
| 5 | 72 | 71 | 3.2 | 3.3 | 226 | 227 | |
| 10 | 74 | 74 | 3.5 | 1.7 | 227 | 238 | >0.10 |
| 15 | 73 | 64 | 3.9 | 1.0 | 225 | 257 | <0.05 |
| 20 | 73 | 57 | 3.8 | 0.4 | 225 | 270 | <0.01 |
| 25 | 73 | 54 | 4.1 | 0.3 | 226 | 275 | <0.01 |

[After Spinazzola & Sherrod (294).]

sure changed from 137 to 116 mm Hg, C_{PAH} increased from 343 to 429 ml per min. The dosage was comparable to the above series. Interestingly, the vasoconstrictive effect of exercise (in patients with mitral stenosis) is counteracted by Apresoline (337).

Serotonin (5-hydroxytryptamine), an extremely interesting compound produces hyperemia in the kidney (64, 294) and has a striking antidiuretic activity. Spinazzola & Sherrod (294) have studied the effects of graded increase in dosage in unanesthetized dogs (table 10). Blood pressure showed no significant changes. Although decrease in GFR contributes to the antidiuresis, some other mechanism may be involved (stage 2). Emanuel *et al.* (83), on the contrary, find that direct infusion into the renal artery in dosage of 10 μg to 100 μg per min increased vascular resistance.

Miscellaneous. Histamine has an unpredictable action on renal blood flow (287). The best work appears to be that of Blackmore *et al.* (22) who administered 2.5 μg per kg per min for 2 hours to dogs. Glomerular filtration rate was constant during the infusion, even though blood pressure fell slowly (never below 75 mm Hg). Control RBF was 360.5 ml per min (SD, 21.5); after 1 hour, 466.5 (± 37.3); 2 hours, 487.8; (± 39.2); recovery, 434.1 (± 34.2). Bradykinin increases direct blood flow in the dog kidney (9), in the face of decreases in systemic blood pressure.

Morphine sulfate (30 mg/kg) results in significant reductions in C_{PAH} in dogs, while C_{In} stays constant. Blood pressure declines slightly but active vasoconstriction is indicated (7).

Xanthine derivatives. In man, theophylline (aminophylline) and caffeine increase filtration rate. After a brief and variable increase in C_D , this suffers a sustained decrease (287). The initial rise is associated with an increase in cardiac output. Parephyllin (diethylaminoethyltheophylline) has no effect on GFR and RBF in dogs. In man, an initial decrease in GFR and C_{PAH} was noted (187), then a slight increase in 20 to 40 min. Filtration fraction showed no change, and blood pressure changes were not significant. In patients in heart failure, GFR and C_{PAH} paradoxically decreased.

ANESTHETIC AGENTS AND RENAL BLOOD FLOW. Several reviews on the subject (242, 275, 287) have pointed out that all general anesthetic agents significantly diminish renal plasma flow, glomerular filtration rate, and water and electrolyte excretion if there is sufficient depth of anesthesia. During light anesthesia, blood flow through the skin and muscles of the extremities may be increased (242) with vasoconstriction in the splanchnic area, which may include the kidney, so that a redistribution of blood occurs. During prolonged or deep anesthesia, flow through skin and muscles, as well as in the splanchnic bed, decreases.

The effects of anesthetic agents are complex, for other factors are introduced which modify the kidney function beyond the direct action of the anesthetic agent itself. Possible changes in systemic arterial and venous pressure would modify renal blood flow. The sympathetic system is stimulated to produce enhanced neurogenic effects. Catecholamine output goes up in turn causing further vasoconstriction. In deep narcosis, effects of hypoxia and hypercapnia enter the picture because of respiratory depression or airway obstruction. In terms of the water and electrolyte picture, changes occur in endocrine output (e.g., enhanced activity of the pituitary-adrenal axis, and increased ADH output from the neurohypophysis). Finally the kidney's ability to correct acid-base disturbances may be impaired.

Pentobarbital anesthesia. During relatively short periods of action, no consistent change in inulin and Diodrast clearances or T_{mD} were noted with dosage of 30 mg per kg (61). When the duration of action of pentobarbital sodium and sodium barbital was increased to 5 hours by Glauser & Selkurt (103), there was 18 per cent decrease in C_{PAH} , with no change in

GFR (C_{Cr}) so that FF increased an average of 24 per cent. Tm_{PAH} was only slightly depressed.

Ether; cyclopropane. Craig *et al.* (67) have shown that light ether and cyclopropane anesthesia (stage III, plane 1) in dogs produced no significant alteration in PAH or creatinine clearance, but in deep anesthesia (stage III, plane 3) depression of function occurred; the PAH and creatinine clearances were reduced to 53 ± 8.9 per cent and 48 ± 7.7 per cent, respectively, of the values observed during light anesthesia, despite maintenance of blood pressure. The clearances returned substantially to normal when the animal was allowed to recover to stage III, plane 1. The reduction was attributed to afferent arteriolar constriction.

Coller *et al.* (56) studied the action of ether and cyclopropane on a series of humans, but their results were complicated by accompanying surgery. However, four with ether showed no significant change in renal blood flow (based on C_D) or glomerular filtration (C_{In}); one showed no change in blood flow but had a marked decrease in GFR; two showed decreases in both blood flow and glomerular filtration. Under cyclopropane, two showed little or no decrease in RBF, yet both showed significant decreases in glomerular filtration. In two others, all renal function was markedly reduced, but these cases were complicated by accompanying shock. Burnett *et al.* (45) reported that in eight patients during ether anesthesia maintained in stage III, plane 2, mannitol clearance was reduced by 21 per cent, and C_{PAH} by 39 per cent, with a resultant increase in FF of 25 per cent. In seven patients receiving cyclopropane, these changes were -31 , -52 and $+35$ per cent, respectively. It is entirely probable that, according to the work of Miles & DeWardener (205), the reductions in RBF resulting from ether and cyclopropane, when they occur, are on a neurogenic reflex basis. Renal vascular resistance increased in dogs inhaling cyclopropane, but in denervated kidneys there was no effect. With ether, an actual fall in RVR occurred in the denervated kidney, evidently a local dilatory mechanism. This was confirmed when ether was injected in the renal arterial flow measuring circuit (rotameter); RVR again decreased, due to active vasodilatation.

AUTONOMY OF THE RENAL CIRCULATION

History

In the preceding sections devoted to extrinsic regulation of renal blood flow (neurogenic and humoral),

the underlying thread of circulatory autonomy was revealed occasionally. Rein (252), in 1931 while studying regional blood flow in dogs during changes in systemic arterial pressure, was struck by the relative constancy of the renal blood flow as compared to other tissues. Unna (316), employing the Rein thermostromuhr, confirmed these observations and concluded: "Es kann die Nierendurchblutung unabhängig von arteriellen Druck reguliert werden." Hartman *et al.* (135) and Opitz & Smyth (238) demonstrated that this obtained under circumstances of reflex alteration in blood pressure (carotid sinus nerve stimulation, carotid clamping) and carbon dioxide inhalation in kidneys that had been denervated, implying an intrinsic mechanism. Enger *et al.* (85) found evidence of autoregulation: partial clamping of the renal artery brought renal flow down, but in a short time there followed a partial restoration of flow. Forster & Maes (91) studied the effects of elevation of mean arterial pressure on the clearance of *p*-aminohippurate (PAH) and creatinine in rabbits whose kidneys had been denervated and whose adrenal glands had been demedullated. They too found that, when blood pressure was elevated by neurogenic mechanisms resulting from clamping of the carotid arteries, these clearances were remarkably constant.

Selkurt (271) plotted the response of blood flow in dogs to progressive decrement of effective perfusion pressure (A-V difference) by lowering arterial pressure (aortic compression) in a "pressure-flow" relationship. This was concave to the pressure axis in a range of 14 to 117 mm Hg with flow relatively independent of pressure at the higher range, but decreasing below ca. 80 mm. Results were essentially the same in the intact as in the denervated kidney. Hemorrhage appeared to abolish the concavity of the pressure-flow relationship. It was not manifested in the dead kidney. The zero flow intercept on the pressure abscissa averaged 14 mm Hg, a minimal yield pressure for movement of blood through the vascular circuits. Selkurt *et al.* (274) further analyzed the pressure-flow relationship of PAH and creatinine clearance and found that glomerular filtration rate manifested good constancy in a range of 90 to 180 mm Hg. This implied that one possible factor in "renal autonomy," a change in vascular resistance due to changes in blood viscosity incurred by filtration at the glomeruli, could be ruled out. Calculations of regional vascular resistance strongly suggested that the afferent arterioles were an important point of control.

Shipley & Study (282) confirmed and extended these observations by examining the renal blood under conditions of elevation of perfusion pressure by a

pump into hypertensive ranges. Above ca. 200 mm Hg, renal blood flow by rotameter increased with increases in perfusion pressure to 280 mm Hg so that a limit to the regulatory mechanism was reached at about 200 mm. Yet GFR remained constant at the higher pressures. DeWardener & Miles (73) confirmed the sigmoid nature of the pressure-flow curve at high pressures and extended the observations on the effect of hemorrhage. The pressure-flow curve during hemorrhage fell markedly below the control curve and assumed approximate linearity; the sustained vasoconstriction had apparently impaired or abolished the autoregulation. Likewise, prolonged perfusion (4–5 hours) also was found to impair autoregulation.

Mechanism of Autoregulation

Possible mechanisms which might account for autoregulation have been explored in several reviews (280, 343, 344). Mechanisms suggested were: *a*) "metabolic theory" or reactive hyperemia theory; *b*) intrarenal vascular reflex control; *c*) changes in viscosity of blood as a factor in changes in renal resistance, the "viscosity theory," as exemplified by the cell separation theory of Pappenheimer & Kinter (240); *d*) the "tissue-pressure" theory, in which changes in arterial, venous, and ureteral pressures in varying degrees create changes in intrarenal pressure, which in turn affect blood flow; and *e*) the "myogenic theory" or vasoconstrictor theory, whereby active changes in the smooth muscles of the arterioles (afferent), in response to changes in intraluminal pressure, regulate flow.

THE "METABOLIC THEORY." This was suggested by Selkurt (280) as a possible explanation for the reduced vascular resistance manifested in the kidney with moderate reduction in perfusion pressure. Increased production, or reduced removal, or both, of (hyperemia-producing) metabolites resulting from the impaired flow and hypoxia, might cause the observed vascular dilatation. Typically, flow drops immediately on decrease in pressure, but improves in 30 sec to 1 min (120, 258). When pressure is released, an "overshoot" occurs, which restores in 30 sec to 1 min. More difficult to explain is the increased resistance which develops when pressure is suddenly raised. If one speculates that a base-line production of metabolites is the case for the kidney, then an immediate increase in flow as pressure is raised might rapidly wash out metabolites responsible for the resting caliber

of the resistance vessels, resulting in a net reduction in caliber. A similar possibility has been considered by Haddy *et al.* (124).

Some support for a metabolic mechanism was offered by the finding that kidneys perfused by pump with hypoxic venous blood demonstrated hyperemia (278), but the possibility of preformed metabolites in the venous blood which might dilate the renal arterioles must be held open. As earlier mentioned, the peculiar flow-limited characteristic of the kidney may make it more susceptible to hypoxic states. Perhaps stronger support was the demonstration by Sarre & Ansorge (262) that the dog kidney exhibited "reactive hyperemia" to short bouts (1–5 min) of clamping of the renal arteries. The responses were usually modest, but in two instances flow increased by 150 and 173 per cent. Flow was restored to normal in these cases in about 5 min. Since a venous outflow method was used, filling of the organ could not have been the apparent cause of the elevated flow on restoration of arterial pressure. It is known that the pH of the cortical substance decreases by 0.3 to 0.4 pH units during partial clamping of the renal artery (237), indicating accumulation of metabolites. Spencer (293) has more recently demonstrated reactive hyperemia in the kidney after brief ischemia; flow, measured with a square-wave electromagnetic flowmeter, was increased in dogs after brief clamping of the renal artery. Contrarily, Grupp & Heimpel (118) more often observed small reductions in flow measured in dogs both by direct arterial inflow and venous outflow following 1 to 7 min of ischemia. In 5 of 26 dogs an increase averaging 16 per cent (maximum, 32%) was seen. Yamada & Åström (352) did not observe reactive hyperemia in the kidneys of cats after brief ischemia. Since abundant evidence exists that the kidney, after more prolonged ischemia, releases pressor material, the complexity of this interesting problem is evident. The duration of ischemia looms as an important variable.

INTRARENAL REFLEXES. Extrinsic reflexes are not necessary for the manifestation of autonomy, and no afferents from renal baroreceptors or chemoreceptors exist according to Page & McCubbin (239). But the presence of intrarenal autonomic ganglia were apparently confirmed pharmacologically: nicotine and dimethylphenylpiperazinium iodide (DMPP) stimulated ganglia and caused the discharge of pressor amines. Page and McCubbin have suggested this as a possible mechanism in autoregulation. Since ganglioplegic and sympatholytic agents have been said to

eliminate the mechanism of homeostasis [Brull *et al.* (38)], the possibility of such an intrarenal reflexogenic mechanism should be weighed, although possible afferent pathways resembling an axon reflex (dendritic mechanoreceptors or stretch receptors) remain to be demonstrated. The results of Brull *et al.*, who argued for an intrarenal reflex mechanism, were somewhat sporadic and complicated by the fact that some of their perfusion pressures after drug treatment were high enough to exceed the normal range of autonomy. Intrarenal sympatholysis with Dibenzylamine (331) and phentolamine (124), tested by abolishing the vasoconstriction produced by DMPP, did not abolish autoregulation.

Procaine injected directly into the renal artery will abolish autoregulation, but this could be an effect directly on the smooth muscle of the arterioles. However, Waugh & Shanks (331) claimed that with procaine concentration of only 50 μg per 100 ml of perfusate, anesthesia of intrarenal nervous elements was achieved without concomitant removal or appreciable depression of vascular smooth muscle responses to direct stimuli. This prevented the vasoconstrictor response of DMPP, but the preparation remained sensitive to small doses of epinephrine or barium chloride. When pressure was elevated by 50 per cent, flow increased only 13 per cent. Furthermore, yohimbine, an adrenergic blocking agent, in concentrations which caused nearly complete intrarenal sympatholysis (as judged by blockade of large test responses to the ganglionic stimulant DMPP and to epinephrine) did not depress autoregulation (331).

Twenty times greater perfusate concentrations of procaine (0.1 g/100 ml) were shown by Waugh and Shanks to abolish autoregulation. In a typical experiment, renal flow increased 64 per cent per 50 per cent increase in arterial pressure. The intense renal vasoconstriction normally evoked by intra-arterial injections of 1 μg epinephrine and 2.5 mg of barium chloride was largely prevented by the higher concentrations of procaine. It is likely that results obtained by Ochwaldt (233) and Weiss *et al.* (333) with comparable dosage of procaine are also the result of marked direct depression of smooth muscle activity.

In summary, the intricacies of distinguishing between abolition of an intrarenal neurogenic component and direct effects on smooth muscle by pharmacological agents are apparent. It would appear, nevertheless, that the evidence offered by Waugh and Shanks weighs heavily against a nervous component.

THE VISCOSITY THEORY. Foremost proponents of this theory are Pappenheimer & Kinter (159, 160, 240) with their cell separation hypothesis, championed by Winton (343, 344). The details are so well known that only a brief review is necessary. In this theory, the interlobular arteries and afferent arterioles act as vessels specially developed to promote plasma skimming and stripping. Streamlining of erythrocytes leaves a core of cells to supply the outer cortical glomeruli. A gradient of red cell concentration would develop, with low cell hematocrit in the deep glomeruli, and high hematocrit in the outer cortical glomeruli. They suppose that the red cells after traversing the glomeruli and efferent arterioles have access to special through channels communicating directly to interlobular veins, leaving a plasma-rich component of the blood to supply the peritubular vascular bed.

Pappenheimer and Kinter believe that the above scheme offers an explanation for the low dynamic hematocrit of the kidney, since the red cells move through the hypothetical shunts faster than the plasma, so that the instantaneous hematocrit of the total renal blood content would be less than the arterial hematocrit value. Support for this was offered by the experimental demonstration in cats that lowered arterial pressure (less streamlining, hence less cell separation) showed higher intrarenal hematocrit.

Autoregulation is brought about by the change in viscosity, increasing in turn resistance to blood flow resulting from hemoconcentration as the blood proceeds to the outer cortex. Such a mechanism could keep total flow constant as a function of the level of arterial pressure. Added facets that are important are as follows: reduction in hematocrit of the perfusing fluid caused remission of autoregulation, and development of a linear P:F relationship, as the theory would demand (160). Implicit in the theory is that a gradient of filtration rate should occur based on the hematocrit distribution, i.e., the inner glomeruli receiving the higher volume of plasma should have the higher filtration rate. A mechanism for autonomy of glomerular filtration rate is offered, for with reduced blood pressure less stripping would occur, so that peripheral glomeruli would have a relative increase in filtration rate, despite the increase in the inner glomeruli.

Incomplete extraction of PAH and Diodrast in dog and man (0.75 to 0.9 respectively), which decreases under a variety of experimental conditions, is explained by the fact that blood passing through shunts is unavailable for extraction. The separation process,

for example, becomes less efficient in the kidneys of anesthetized animals, thus leading to correspondingly lower extraction ratios. With lowered hematocrit, more plasma passes through the hypothetical shunt circulation, bypassing the tubular elements. A reduction in extraction ratio to 60 per cent of control value was noted under this circumstance (160).

The peculiarities of oxygen supply to the kidney, resulting from the implications of this hypothesis, have been discussed earlier. In brief, the peritubular circulation is supplied with a cell-poor component of blood, and the oxygen saturation in blood leaving the actively metabolizing tissue of the kidney may be far lower than in the renal vein. This was proposed as the basis for the flow-limited nature of the organ despite high venous oxygen content, a proposal challenged by Levy (178, 179).

The provocative cell-separation theory has served a useful purpose in stimulating a sizable amount of research. From this has grown a considerable body of data which has challenged several of the fundamental precepts of Pappenheimer and Kinter. These facts are summarized:

1) In the first instance, the hypothetical short shunt from the efferent arterioles to interlobular vein, bypassing the peritubular capillaries, has never been anatomically demonstrated. While the vasa recta circuit might conceivably function in this role, it is a long circuit with a slow circulation and is low in erythrocytes, not cell-rich as the hypothesis demands. In all probability, less than 10 per cent of the total renal blood flow passes through this circuit, based upon the extraction ratio of PAH (256), and the flow estimates of Kramer *et al.* (166); hence its role in autoregulation is dubious.

2) Studies of cell-plasma transit time show no great differences in speed of red cell transit compared to labeled albumin, hence do not favor the idea of preferential shunting.

3) Studies of distribution of erythrocytes through the zones of the kidney reveal no increase in concentration from outer medulla to cortex.

4) Autoregulation can persist with anemia (305, 330) or with perfusion of kidneys with cell-poor fluids, e.g., dextran (143, 306, 308, 330, 331, 333). But in support of Pappenheimer & Kinter (240), Haddy *et al.* (124) saw no autoregulation in kidneys perfused with dextran. Autoregulation, when initially present, has been shown by Waugh and Shanks to disappear after perfusion of the kidney with dextran for variable periods of time. Of considerable interest is the finding that a plasma factor is needed in order to maintain

satisfactory autoregulation (330) and may explain some of the differences in results.

5) The cell-separation hypothesis must necessarily advocate differential filtration in glomeruli at different levels, highest in the juxtamedullary, lowest in the peripheral. From this a "splay" in the Tm_G titration curve could be expected, whereby nephrons attached to glomeruli with high filtering capacity would be saturated first, those with low filtration last. No such splay was observed in anemic dogs (158) and humans (256), indicating that all nephrons are saturated approximately simultaneously.

6) When few or no red cells are present in arterial blood the proportion of plasma flowing through the preferential channels should increase with increasing pressure, and hence E_{PAH} and E_D should decrease in anemic animals at the higher flow of elevated pressure (159). This was found to be the case in cats. According to Kinter and Pappenheimer, this would not occur when red cells are present because the tendency for plasma flow through the shunts to increase, owing to the distensibility factor, would be counteracted by more efficient plasma skimming. On the other hand, Thompson *et al.* (305) found no significant effect on E_{PAH} of variations in blood pressure in either normal or anemic dogs.

7) The appearance curves of PAH in the urine of normal and anemic subjects are superimposable, suggesting no difference in traversal pathway (256).

In summary, the numerous weighty arguments which have been raised in opposition to the cell-separation hypothesis appear to necessitate abandonment of this theory as being important in explaining renal autonomy, although Winton (344) has taken the view that it may be a participating mechanism in the over all phenomenon.

TISSUE PRESSURE THEORY. Advocates of this theory must of necessity demonstrate an increase in IRP as arterial perfusion pressure is elevated. Such evidence has been offered by Hinshaw *et al.* (141-144) for the isolated kidney-lung-pump preparation. Representative experiments are shown in figure 25 (143). It is seen that stabilization of flow coincides with an abrupt rise in IRP at ca. 80 mm Hg. Although flow with dextran is higher, because of lower viscosity, the same relationship prevails. In another study (142), it was shown that kidney weight increased with pressure, 0.6 g per 10 mm Hg rise before onset of autoregulation (range 40 to 80 mm) and only 0.3 g per 100 mm Hg after. Thureau & Kramer (307), as well as Seher (265), observed a weight increase with sudden

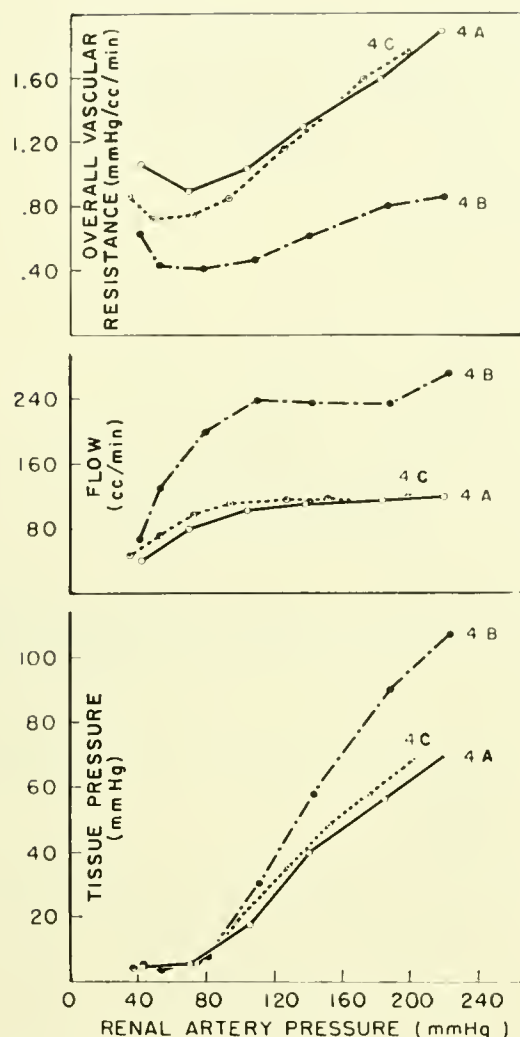


FIG. 25. Renal circulatory autonomy in the dog as a function of tissue pressure (needle puncture). Symbols 4A and 4C represent curves obtained with blood perfusions before and after 4% dextran (4B). [After Hinshaw *et al.* (143).]

increase in pressure. It was concluded that the autoregulation occurred because of increased accumulation of extravascular fluid resulting from enhanced filtration at high pressure, which compressed low pressure vessels. Significantly, blood volume estimated from mean transit time ($T-1824 \times \text{mean blood flow}$) was shown to decrease slightly at pressures in the range 100–200 in the autoregulating kidney (188), but volume increased in the KCN poisoned kidney. Hence the weight change is likely due largely to extravascular fluid accumulation.

Analysis of regional resistance changes has been attempted by Hinshaw *et al.* (145), on the basis of certain assumptions. The first was that a stabilized ureteral pressure after occlusion was a measure of

the Bowman's capsule extravascular pressure. Then, glomerular capillary pressure should equal this pressure plus the plasma oncotic pressure (20 mm Hg in this series). Another assumption was that intrarenal venous pressure (postperitubular capillary segment) was equal to tissue pressure (IRP), (which has been shown to be correct for the arcuate veins at elevated venous pressure) plus the plasma oncotic pressure. The authors have formulated the regional resistances as follows [reprinted with permission from Hinshaw *et al.* (145)]:

$$\begin{aligned} \text{PRE-GLOMERULAR SEGMENT} \\ &= \frac{\text{RA} - \text{UP} - \text{COP}}{F} \end{aligned}$$

POST-GLOMERULAR SEGMENT

$$\begin{aligned} \text{(a) EFFERENT ARTERIOLAR SEGMENT} \\ &= \frac{\text{UP} - \text{TP}}{F} \end{aligned}$$

$$\begin{aligned} \text{(b) POST-PERITUBULAR CAPILLARY SEGMENT} \\ \text{(VENOUS SEGMENT)} \\ &= \frac{\text{TP} + \text{COP} - \text{RV}}{F} \end{aligned}$$

RA = RENAL ARTERY PRESSURE UP = URETERAL PRESSURE
TP = TISSUE PRESSURE COP = COLLOID OSMOTIC PRESSURE
RV = ORIFICE RENAL VENOUS PRESSURE

Autoregulation was shown to persist during occlusion of the ureters (144), as indeed it does during venous pressure elevation (119, 123, 281). The above estimates of regional resistance are applicable, then, to the autoregulation manifested during ureteral occlusion in the isolated perfused kidney. In a range of 100 to 191 mm Hg renal arterial pressure the following average changes occurred: preglomerular resistance, -4 per cent; postglomerular, +101 per cent (in the latter value, most is attributable to the postperitubular capillary segment). Under these special circumstances, afferent arteriolar control seems unimportant, and it is the influence of increased IRP on compressible postglomerular vessels that appears to dominate.

Although this hypothesis is ingenious in its application, the special circumstance of the measurements will make it difficult to apply to the normally functioning kidney. It is well to recall that the fundamental precept, i.e., that IRP varies with arterial pressure, has not been uniformly accepted by all investigators.

If the above hypothesis is correct, decapsulation of the kidney should have a significant influence on the autoregulatory mechanism. In this, investigators are not in agreement. Bounous *et al.* (28) after careful

decapsulation procedures, found that autoregulation was indeed abolished (fig. 26). Haddy *et al.* (124) illustrate several experiments which offer support of this: two pressure-flow curves are more linear after decapsulation than before. But Miles & DeWardener (206) found no difference between the IRP of the control and that of the decapsulated kidney. Elevation of IRP by mannitol diuresis and elevation of venous pressure caused approximately equal increases in IRP in the decapsulated kidney and in the paired control. In an extreme situation, following KCN treatment and elevation of perfusion pressure by pump to 300 mm Hg, IRP increased ca. 100 mm Hg in both control and decapsulated kidneys.

In summary, the tissue pressure theory is attractive in some respects, but since it concerns a purely physical mechanism it is hard to square with the lack of autoregulation in kidneys treated with procaine, KCN, and papaverine, in the oil-perfused kidney, or even in dead kidneys. Implicitly, it dispenses with the need for afferent arteriolar control, but a considerable body of evidence supports the possibility of such control.

THE MYOGENIC THEORY. The principal evidence for this theory comes from the behavior of the renal blood flow during rapid changes in perfusion pressure. An example taken from the work of Semple & DeWardener (281) appears in figure 27. Flow was measured with an electromagnetic flowmeter. Note

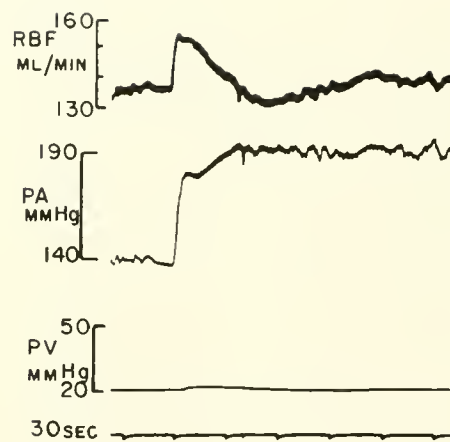


FIG. 27. Renal circulatory adjustment following sudden increase in arterial perfusion pressure (PA). PV: renal venous pressure. [After Semple & DeWardener (281).]

the immediate "overshoot" of flow as pressure is raised, followed by return to a flow level somewhat below the control within 60 sec, and then stabilization at the control flow but at a pressure some 50 mm Hg higher than during the control. On occasion, rhythmic rapid fluctuations in flow were observed after pressure elevation before stabilization occurred, a "hunting" phenomenon.

When the elevation was done in progressive steps, the overshoot was proportional to the pressure elevation, but returned in each instance to approximate the control level [see fig. 28 (308)]. It is of interest that the levels of flow, reached instantaneously after pressure change, fall on a curve describing the pressure-flow relationship in the same kidney after paralysis of smooth muscle activity with papaverine (\times — \times in the figure).

Likewise, when pressure was dropped in steps, flow decreased immediately in a passive manner, but in 30 to 60 sec readjusted to the previous level [fig. 29 (120)]. In this series, constancy of flow was maintained down to 70 mm Hg, then fell off rapidly.

Thurau & Kramer (307) have analyzed in an interesting fashion the correlation of total blood flow, superficial (cortical peritubular) capillary blood content, and weight change in response to rectangular pressure increments. The results are illustrated in figure 30. Capillary blood content was measured by an "infrared reflectometer" technique. Note the typically instantaneous overshoot of flow as pressure is increased, followed by stabilization. (Allowance must be made for the possibility that an overshoot artifact by the rotameter may contribute to the initial rise.) This appears to be a function of the initial tonus

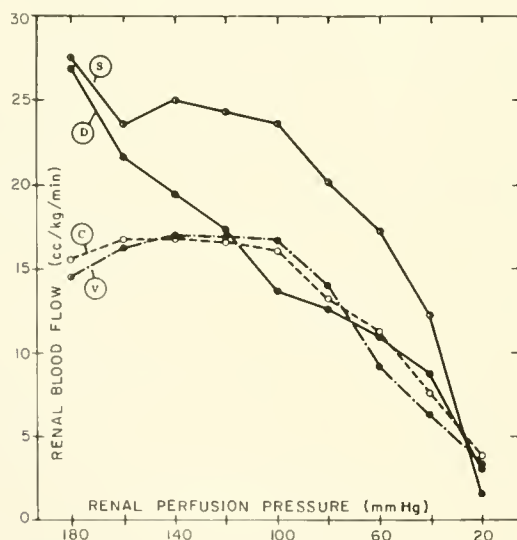


FIG. 26. Effect of decapsulation on autoregulation in the dog. C: control; V: bilateral section of cervical vagosympathetic chains in the neck; S: renal denervation; D: renal decapsulation. [After Bounous *et al.* (28).]

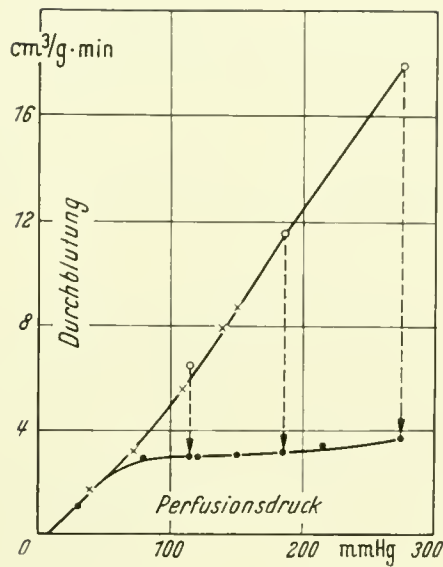


FIG. 28. Immediate and stabilized relationship of renal blood flow to perfusion pressure. [After Thureau & Kramer (308).]

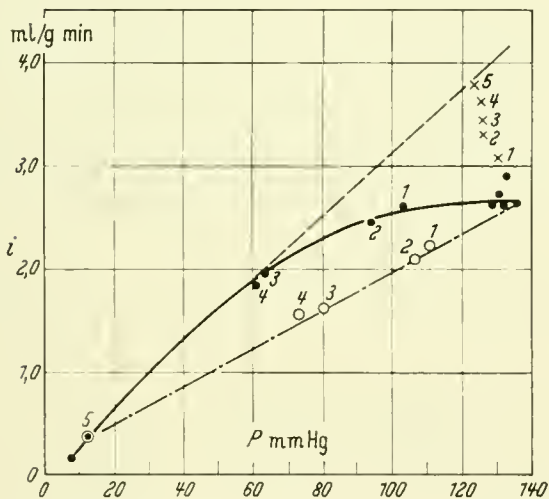


FIG. 29. Immediate and stabilized response of renal blood flow to decrease in perfusion pressure. ○: Immediate flow; ●: stabilized flow; ×: immediate response to restoration of pressure, then return to control (●) cluster, at upper end of curve. The numbers indicate sequence of response. [After Grupp *et al.* (120).]

of the vascular smooth muscle; when low, overshoot was greater than when tonus was high. The capillary volume increases transiently during the phase of overshooting (increase is with downward deflection of the galvanometer) accompanying the initial passive expansion of arteries and arterioles as pressure is suddenly increased. Then, as total flow settles to

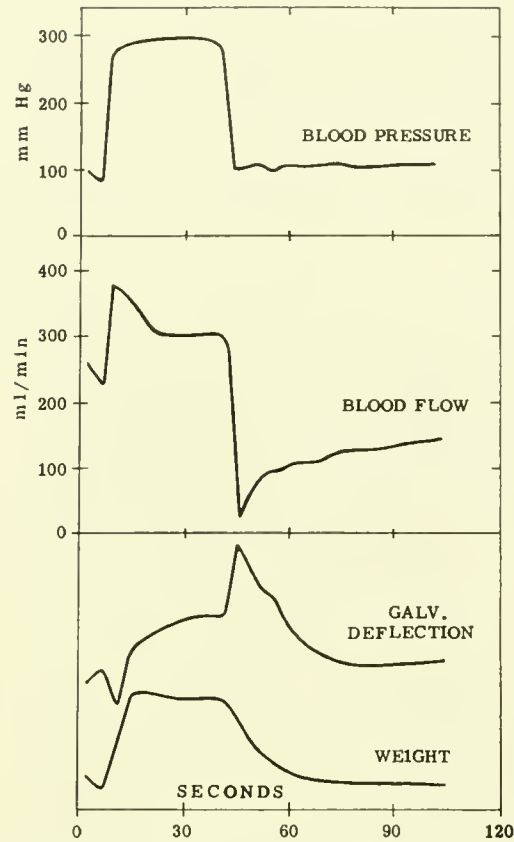


FIG. 30. Immediate and delayed adjustment to rectilinear increase in blood pressure—renal blood flow, superficial cortical blood volume (galvanometer deflection)—and kidney weight. (Downward deflection of galvanometer indicates increase in volume.) Weight change is an approximation of trend. [After Thureau & Kramer (307).]

lower levels after the onset of the myogenic contraction, capillary content decreases somewhat.

Upon decrement of pressure, flow decreases markedly below the control, indicative of the contracted state of the resistance vessels. Then normal flow is slowly restored as the myogenic response recedes. Capillary blood content during this decrement in flow also decreases significantly, then is restored as total flow rises.

The weight change may show a triphasic response in experiments with more prolonged stages: *a*) an initial rapid increment as blood surges into the relaxed vessels; *b*) a transient drop as the myogenic response occurs; and *c*) a secondary rise. The last may be the result of increased transudation of fluid through the capillaries at the elevated pressure and increased flow.

The dynamic reactivity implied in these fairly rapid adjustments corresponds to the type of reac-

tivity anticipated from the smooth muscle of the vasculature. That a vital phenomenon is involved is supported by the action of a number of agents known to impair smooth muscle activity: papaverine will eliminate autoregulation (306, 308), as will KCN (188, 207, 233) and theophylline (121). Procaine has been cited earlier. Certain anesthetics, such as numal (120, 121) and chloralhydrate (330) impair autoregulation as will ethanol (260).

Both cooling and perfusion of the kidney with oil remove autoregulation (328, 330). Hemorrhage depresses autoregulation (73, 271, 331). Anoxia created by perfusion of the kidney with perfusion fluid [20% plasma-80% polyvinylpyrrolidone (PVP)-Locke's solution] subjected to helium rather than oxygen appeared to impair autoregulation somewhat; flow increased more with pressure increments than with comparable increments during the control (331).

It is well to point out that autoregulation may be impaired in another manner and may, in part, explain the apparent loss of response in hemorrhage. Under this circumstance and with adrenaline and hypertonic fluid infusions, the smooth muscle of the vasculature becomes highly tonic, and responses to increments in pressure become much reduced (307). Then the pressure-flow curve becomes convex to the pressure axis and resembles the pressure-flow curves obtained in the hind limb and other organs, which usually have a higher resistance than the kidney.

ABERRANT RESULTS. Several investigations may be cited in which typical autoregulation was not observed, but in which pressure-flow curves were linear or convex to the pressure axis. This includes the work of Ohler *et al.* (235) in the rat. Indications of a high degree of vascular tone are seen in the low flows in many preparations and the high flow intercepts on the pressure axis. It will be recalled that others have reported the more common concave-to-pressure-axis curve in the rat (333), indicating autoregulation.

Likewise, the work of Langston *et al.* (172, 173) manifested a convex-to-pressure-axis relationship of flow in dogs. Again, flow per gram of tissue was low (less than 2 ml/min/g) at normal pressure, suggesting a highly tonic preparation. The high pressure intercept for flow also suggested this. In the first report (172) flow appeared to be only about 10 ml per min (total per kidney) at 60 mm Hg. In the second report (173), in the control series, the zero flow intercept lay between 20 and 40 mm Hg; flow at 100 mm Hg in most preparations was less than 1.5 ml per min per g. Furthermore the method of perfusion suggested the

possibility of a source of technical error. The kidney was perfused via an isolated segment of aorta at the level of the renal artery. Hardin *et al.* (130) used a similar technique, and found the same convex relationship. However, when they carefully tied small lumbar arteries leaving this segment of the aorta, the pressure-flow curve assumed the more commonly found contour, concave to the pressure axis (fig. 31).

SIGNIFICANCE OF THE MYOGENIC RESPONSE. Bayliss (13), a number of years ago, called attention to a myogenic response to sudden changes in pressure both in denervated organs and segments of artery (carotid), and attributed it to alterations in tonus of smooth muscle in the arteries in response to change in tension. Wachholder (324) studied isolated segments of equine carotid, and observed contractions following sudden increases in pressure occurring with a latency of usually 10 to 20 sec (8 sec was the shortest). The contraction phase lasted 20 to 60 sec. Bürgi (44) utilized bovine mesenteric artery segments, but saw distinct responses in only 23 per cent of his tests; weak responses occurred in 9 per cent, and in 12 per cent the response had so great a latency that it was deemed questionable; 56 per cent showed no response.

Folkow (89, 90) has placed the suggestion of Bayliss and others on a firmer footing. His experiments, utilizing the dog hind limb preparation, under conditions which apparently controlled possible neurogenic

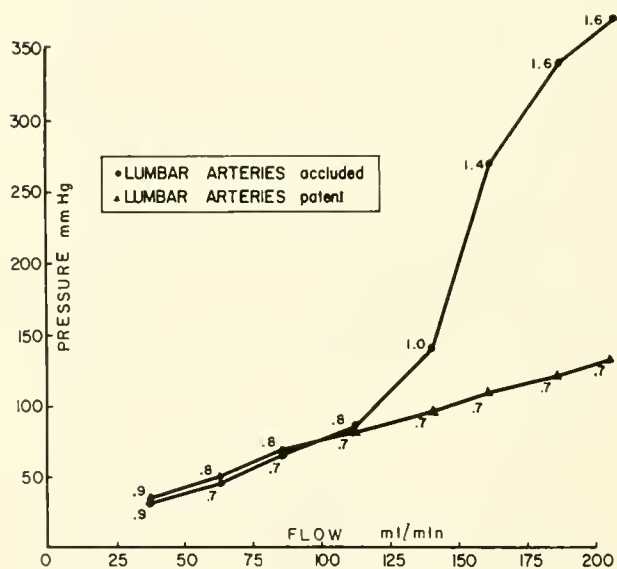


FIG. 31. Perfusion pressure as a function of rate of blood flow through both kidneys of a dog before and after occlusion of the lumbar arteries. Numbers are renal vascular resistance in mm Hg/ml/min. (After Hardin *et al.* (130).]

and humoral factors, gave support to the myogenic theory, and he concluded "Vascular tone is in its basic origin myogenic, though strongly influenced by external factors."

That this property of the smooth muscle of the kidney arterioles is typical of smooth muscle elsewhere is shown by the work of Bozler (30). Isolated segments of ureter were subjected to sudden increases in internal pressure. This created electrical potentials which produced, at first, local responses; if the potential was strong enough, a conducted response resulted. He found that the greater the pressure, the steeper was the local potential change and the shorter the delay for the onset of conduction. Bulbring (43) has shown that stretch of smooth muscle cells of the taenia coli acted as a stimulus for increased myogenic automaticity, and that the element of the smooth muscle cell sensitive to stretch was closely combined with the properties of the tension-producing element.

The group of investigators that support the myogenic theory to explain autoregulation of the kidney favor the afferent arteriole as the site of regulation. More specifically, the myocytes of the juxtaglomerular apparatus appear to be a likely point of control (274, 331). In conclusion, the myogenic theory seems most attractive as an explanation of autoregulation of the renal circulation, but it is likely that acceptance of one theory to the exclusion of some of the others would be an oversimplification. The challenging prospect remains to integrate properly the several possibilities into a unified concept which might operate in the intact, unanesthetized animal in normal circulatory homeostasis.

PRESENT STATUS OF THE TRUETA JUXTAMEDULLARY SHUNT

It was postulated by Trueta *et al.* (311) that diversion of renal blood from its usual cortical route to the "less resistant and more capacious medullary circuit" (198) (probably not true by currently known facts) was a physiologic mechanism which was involved in a number of abnormal circulatory states. These included reflex anuria, anuria associated with incompatible blood transfusion, crush injury, blackwater fever, etc., Pitressin inhibition of water diuresis, the renal ischemia of shock or that induced by fright or adrenaline, in the reduction in tubular excretion following protracted renal ischemia, and in the genesis of essential hypertension.

These investigators had reported that during renal

ischemia the arterial pulse may be seen in the renal vein, and that the renal venous blood may acquire an arterial color. It was their belief that the juxtamedullary glomeruli and vasa recta circuit may afford veritable shunts between the renal artery and vein "... a diversion of blood from the cortex, the most active part of the kidney, to the medullary pathway, with a possible increased speed of flow through these channels."

Such shunts should therefore cause a reduction in renal oxygen A-V difference. Furthermore, this would shunt blood away from the zone of greater metabolic activity in the cortex to the juxtamedullary vasa recta and loop of Henle system, with less efficient perfusion of the proximal tubular secretory sites. This should cause a decrease of E_D or E_{PAH} with an increase, or no necessary decrease, in total blood flow as measured by direct methods or perhaps by the Fick method. Finally, if shunts open which bypass glomeruli, E_{In} should decrease without a decrease in blood flow, or should decrease more markedly than blood flow (assuming continued adequacy of filtration pressure).

Morphological identification of the shunt should be possible with injections of India ink, Prussian blue, or radiopaque material such as Thorotrast. The Trueta evidence consisted mainly of appearance of India ink or Thorotrast in higher concentration in the juxtamedullary region when injected intravascularly during sciatic nerve stimulation or epinephrine action. But great care must be exercised in attempts to interpret rate or volume of flow by appearance of the injection mass. Thus, contraction of venous effluent constrictors could give the appearance of congestion of the medullary circuit, in the face of an actual reduction of flow. Incomplete filling due to faulty injection could give the appearance of vasoconstriction in the cortex.

Morphological Evidence

Injection studies have been controversial, being interpreted either in favor of the original hypothesis or against it. This has been largely a matter of interpretation of what are often quite similar pictures.

Montague & Wilson (214), correlating Thorotrast injection studies with clearance data (E_{PAH}) in rabbits, believed they saw evidence of a juxtamedullary shunt after epinephrine injection. This was accompanied by marked decreases in E_{PAH} (mostly negative, and averaging -26.6%). Herdman & Jaco (138) partially constricted one renal artery of rabbits, and injected India ink 3 days to 5 weeks later. They found the ink chiefly in the inner cortex and juxtamedullary

zone, suggesting the diversion of blood accompanying cortical ischemia. Tracheal occlusion in rabbits (92) caused paling of the kidney and decrease in volume. Sections of innervated kidneys removed at the height of anoxia showed anemia of the cortical portions. In the denervated, there was no such "diversion" of flow, but it was possible to produce it in these by injections of epinephrine. Arcadi & Farman (2) state that in rabbits, blood was diverted almost exclusively to the cortical circuit by pilocarpine and magnesium sulfate injection and most prominently by water diuresis. Dehydration, on the other hand, caused the accumulation of ink in the medulla. The findings of Kuhlitz (168) in rats were very similar with respect to the findings on diuresis and dehydration. Moyer *et al.* (222, 223) although finding uniform distribution of India ink in dog and rabbit kidneys during sciatic stimulation, nevertheless report cortical ischemia and subcortical accumulation of ink after injection of 0.2 mg of epinephrine into the rabbit, but this finding does not have to be interpreted as demonstrating the opening of medullary shunts.

Insull *et al.* (150) have pointed out that an adequate filling pressure is needed for validity of the injection methods. When Prussian blue was injected into fresh rabbit kidneys at a pressure of 50 cm H₂O, good filling of the entire kidney, including cortex, was observed; at 25 cm H₂O, filling of the juxtamedullary glomeruli and vasa recta only occurred.

In some experiments involving sciatic stimulation, stimulation of the perirenal plexus, or hemorrhage, the juxtamedullary glomeruli were uniformly stained, while the peripheral glomeruli were not. This occurred only when renal blood flow was low. They interpreted this as regional cortical ischemia but not as increased flow through the medulla.

The conclusions of Block *et al.* (24) and Kahn *et al.* (156) are similar. Block *et al.* tried stimulation of renal nerves in rabbits, clamping of the artery, injection of constrictor agents, and sciatic nerve stimulations. They concluded that a pale cortex and a medulla filled with blood were not evidence that blood was flowing largely through the medulla; the medulla may be congested even though flow has stopped. Kahn *et al.* found during sciatic stimulation in the rabbit a normal distribution of ink in 8 of 11 animals. In 3, however, the peripheral cortex had no ink, and the juxtamedullary glomeruli and the medullary vessels were well filled.

In summary, the rabbit kidney during various types of strong afferent stimulation or during epinephrine action may demonstrate a cortical ischemia, with

maintained flow in the medulla. This cannot be interpreted as diversion of flow to the medulla, and particularly not as increased flow through this zone. Nevertheless, the anatomical evidence of a dual circulation is good, and there is some good functional evidence of this.

Daniel *et al.* (69) have made excellent serial angiograms in cats and dogs which follow the progress of Thorotrast through the kidney. The material passes very rapidly through the cortex, but the diffuse shadow of the medulla persists long after the veins have emptied, demonstrating a much slower perfusion of the vasa recta system of the medulla. This conforms with the studies of Kramer *et al.* (166) who used a photoelectric technique. They bring evidence that the role of the medullary vasa recta system may be unique in connection with the role of the counter-current system, and the dilution and concentration of the urine. Other evidence is at hand in support of this, and will be taken up in a later section.

Functional Evidence: Interpretations Based on Clearance Data

Scher (264) used a heated-thermocouple technique in dogs, rabbits, and cats, one thermocouple being placed in the cortex and the other in the medulla. Although quantitative interpretations must be made cautiously, focal flow paralleled total renal blood flow during action of epinephrine and arterenol, acetylcholine, and stimulation of periarterial plexus.

The clearance data are concerned mainly with changes in A-V oxygen difference, and in E_{PAH} and E_{In} . Moyer *et al.* (223), during marked reduction in flow (-46%) resulting from prolonged sciatic stimulation in dogs, found the A-V oxygen difference increased from 1.7 to 3.3 vol per cent; in rabbits, from 3.1 to 6.8 vol per cent in a group in which venous flow was measured, and 3.5 to 9.2 vol per cent in a venipuncture group. With epinephrine, resulting in increased blood pressure and reduced flow (as much as 70% reduction) in rabbits, A-V oxygen increased as much as 313 per cent. Other investigations detected no significant alteration of oxygen extraction in dogs or man during epinephrine injection (149, 224, 254).

Epinephrine in dogs gave no evidence of a medullary shunt, since E_{PAH} , E_{Cr} , extraction of oxygen and Tm_G did not significantly decrease in presence of moderate to marked decrease in GFR, urine flow, and RBF (149). Moyer & Handley (224) observed no reduction in E_{PAH} in dogs, but Tm_G decreased due to

TABLE 11. *Effect of Albumin Infusion on Renal Function in Man*
[75 g Alb. (300 ml) infused in 10-24 min]

| | Before | | | | | After | | | | | % Increase | | | |
|-------------------|-----------------|------------------|-----------|------------------|----------|-----------------|------------------|-----------|------------------|----------|-----------------|------------------|-----------|----------|
| | C _{in} | C _{PAH} | Total RPF | E _{PAH} | Med. RPF | C _{in} | C _{PAH} | Total RPF | E _{PAH} | Med. RPF | C _{in} | C _{PAH} | Total RPF | Med. RPF |
| Normal | 165 | 863 | 1044 | 82.7 | 181 | 189 | 1123 | 1586 | 71.2 | 463 | 14 | 31 | 52 | 256 |
| Normal | 112 | 741 | 820 | 90.4 | 79 | 124 | 1001 | 1280 | 78.3 | 279 | 11 | 35 | 56 | 354 |
| Normal | 130 | 638 | 788 | 81.0 | 150 | 138 | 764 | 1250 | 61.0 | 486 | 6 | 20 | 59 | 324 |
| Hypertension | 109 | 375 | 429 | 87.3 | 54 | 112 | 491 | 662 | 74.3 | 171 | 3 | 31 | 54 | 316 |
| Hypertension | 100 | 542 | 657 | 82.5 | 115 | 103 | 693 | 938 | 73.7 | 245 | 3 | 27.5 | 43 | 213 |
| Hypertension | 36 | 145 | 250 | 58.0 | 105 | 39 | 154 | 353 | 43.6 | 199 | 8 | 6 | 42 | 190 |
| Chronic nephritis | 56 | 265 | 413 | 64.0 | 148 | 32 | 240 | 533 | 45.1 | 293 | -43 | -9.0 | 29 | 198 |
| Nephrotic synd. | 66 | 444 | 493 | 90.0 | 49 | 110 | 757 | 1010 | 75.0 | 253 | 67 | 70 | 205 | 516 |
| | | | | | | | | | | Avg. | 86 | 26.5 | 67.5 | 296 |

Total RPF (total renal plasma flow) = $(C_{PAH}/E_{PAH}) \cdot 100$.
C_{PAH}. [After Cargill (48).]

Med. RPF (medullary renal plasma flow) = Total RPF -

glomerular closure during epinephrine and arterenol infusion. Epinephrine and histamine caused a decrease in E_{PAH} of only 11.4 per cent at the maximum in the human (254). Tilting, with resultant increased sympathetic activity as evidenced by reduction in RPF ($C_{PAH} \cdot E_{PAH}$), induced no change in E_{PAH} (39).

An interesting exception, and at present the only type of positive evidence of increased flow through the medullary circuit, is supplied by Cargill (48) on the effects of iv administration of serum albumin on renal function of human subjects in water diuresis. The results are summarized in table 11. Note that E_{PAH} decreased and the calculated medullary plasma flow increased from 110 to 298 ml per min. Michie *et al.* (204) have supplied excellent confirmation of these results. In their studies, the constancy of Tm_G and Tm_{PAH} suggested that no nephrons were shut off as RPF increased up to 200 per cent. They suggested that this was due to opening of intrarenal shunts without diversion of cortical blood. Barker *et al.* (11) concur with the observations of Michie *et al.* They found also that A-V oxygen decreased by 30 to 40 per cent as the total renal blood flow increased, a fact consonant with the above interpretation.

Role of the Medullary Circulation in Diuresis and Antidiuresis

The Oxford workers originally suggested juxta-medullary diversion of blood, with diminished filtration and greater reabsorption of water in the thin segment, as a mechanism explaining the antidiuretic action of Pitressin, spontaneous changes in urine flow in the erect and supine position, during emotional

excitation, and in other circumstances involving endogenous ADH secretion. The medullary diversion of blood was first proposed as an explanation of anti-diuresis by Frey (96) in 1934.

From this it has been assumed by Maxwell *et al.* (198) that changes in E_{PAH} should accompany diuresis. This was not the case in a series of human subjects presented by them with a range of urine flow from 0.68 to 19.7 ml per min. E_{PAH} remained within a normal range of 0.88 to 0.96. However, their observations of entire diuretic cycles were few. Furthermore, inhibition of water diuresis with doses of Pitressin as high as 2000 to 5000 milliunits per hour caused no significant alteration in E_{PAH} , E_{in} , and A-V oxygen difference.

The application of the intrarenal photoelectric technique for measuring regional dye transit time (T-1824) has disclosed interesting new facts about this mechanism. The technique as applied by Kramer *et al.* (166, 309) is shown in figure 32. Normally, mean transit time averages 27.7 sec for the medulla, and 2.5 sec for the cortex of the canine kidney. When the perfusion pressure was elevated (carotid sinus denervation and vagal block by narcosis, or by pump), medullary transit time was markedly reduced, while cortical transit time and total renal blood flow (rotameter) remained constant. With this, urine volume increased noticeably. Two representative experiments appear in table 12 (308). From such evidence, they conclude that the juxtamedullary glomeruli and the vasa recta system do not demonstrate autoregulation of flow. (It is possible that enhanced perfusion of the medulla at higher pressure via shunts of other types, e.g., the spiral arteries, arteriolae rectae verae, or

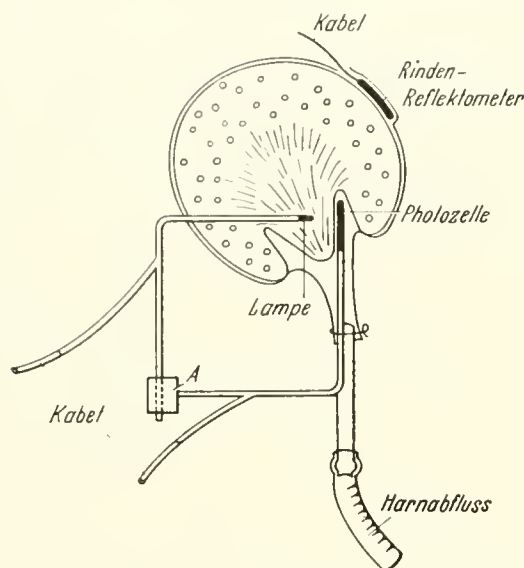


FIG. 32. Method for measuring cortical and medullary circulatory transit time. [After Kramer *et al.* (166).]

TABLE 12. Effect of Increased Perfusion Pressure on Regional Transit Time of the Kidney

| Renal Art. Pressure mm Hg | Med. Trans. Time (\bar{t}_{pM}) sec | Cortical Trans. Time (\bar{t}_{pR}) sec | $\frac{\bar{t}_{pM}}{\bar{t}_{pR}}$ | Blood Flow ml/g/min | Urine Vol. ml/min |
|---------------------------|-----------------------------------------|---------------------------------------------|-------------------------------------|---------------------|-------------------|
| Experiment 7 | | | | | |
| 105 | 16.5 | | | 4.2 | 0.25 |
| 195 | 12.1 | | | 4.5 | 2.50 |
| 205 | 11.2 | | | 4.5 | 3.50 |
| Experiment 11 | | | | | |
| 140 | 32.3 | 3.1 | 10.4 | 4.1 | 0.30 |
| 165 | 27.5 | 3.3 | 8.3 | 4.0 | 0.75 |
| 210 | 22.9 | 3.1 | 7.4 | 4.3 | 2.25 |

[After Thureau *et al.* (308).]

Ludwig's arterioles, could produce this effect.) The total volume flow, they contend, is small relative to total flow, and is within the error of the method of measurement. Nevertheless, it suffices to "washout" the osmotic gradient established in the critical long vasa recta loops and accompanying loops of Henle in the papillary zone. With this, the mechanism for concentration of the urine becomes limited; and diuresis ensues. Selkurt (276) has shown that this type of diuresis is accompanied by enhanced sodium excretion.

In support of this hypothesis are the effects of water diuresis and ADH action (fig. 33). Note the marked decrease in medullary-plasma transit time (\bar{t}_{pM}) with diuresis, and the return during ADH action.

These effects are thought to be the result of changes in blood viscosity brought about during water diuresis (decreased concentration of albumin and cells in the vasa recta) or increased ADH action. It will be recalled that with water diuresis, lack of ADH activity permits the urine to remain hypotonic: the osmotic gradient is dissipated and, with it, no concentration of blood constituents occurs: blood viscosity decreases, and transit time is reduced. The vasopressor activity of ADH (arginine-vasopressin) may conceivably be involved in regulation of blood flow in this circuit.

The critical point of change in \bar{t}_{pM} occurs when $C_{OSM} - I' = 0$, as revealed in two representative experiments in figure 34. When free water clearance (C_{H_2O}) begins, \bar{t}_{pM} reaches a rather constant, minimal value.

The failure of Maxwell *et al.* (198) to note changes in E_{PAH} with diuresis and antidiuresis may have occurred because the above changes in flow are small enough not to be discernible in the normal range of variation of the E_{PAH} measurement.

An explanation of the results of Goodyer *et al.* (108, 109) may fall into line with the above findings. During nonshocking hemorrhage during which arterial pressure was kept constant, sodium excretion declined in the absence of measurable changes in glomerular filtration rate or renal plasma flow. (Data on urine volume were not supplied, but this must certainly have declined.) Measurement of intrarenal hematocrit led them to conclude that intrarenal redistribution of blood flow may have occurred, involving diversion of plasma to cell-poor capillaries (or to lymphatic spaces). This could involve the above mentioned vasa recta mechanism, and obviously would be the converse of the above cited experiments involving increased renal perfusion pressure.

In summary, a newly recognized and important function of the vasa recta system as a counterpart of

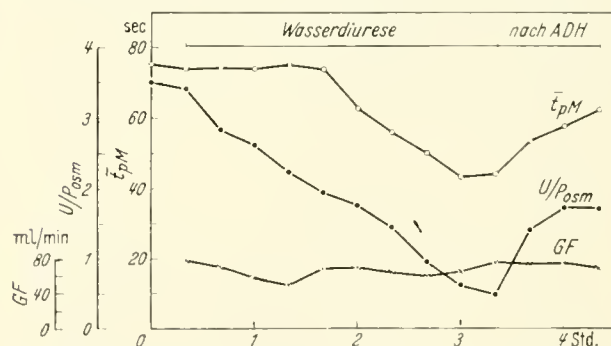


FIG. 33. Mean medullary transit time of T-1824 (\bar{t}_{pM}) during diuresis and after ADH; U/P_{osm} : osmolar concentration ratio of urine to plasma; GF : glomerular filtration. [After Thureau *et al.* (309).]

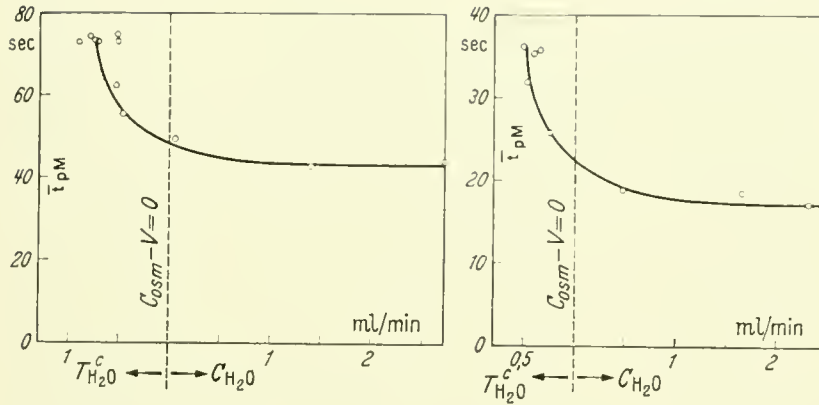


FIG. 34. Mean transit time during diuresis and antidiuresis as a function of CH_2O (water concentration); $T_{\text{H}_2\text{O}}^c$: osmotic water deficit, i.e., below equilibrium point. [After Thureau *et al.* (309).]

the loop of Henle in the countercurrent system is indicated, and this becomes the modern role of the former Trueta juxtamedullary shunt.

RESPONSE OF RENAL BLOOD FLOW TO PHYSIOLOGICAL STRESS

Exercise

The dog and man differ significantly in the response of the renal blood flow to exercise. The canine kidney shows a considerable amount of autonomy of circulation during exercise to a degree which results in significant reduction in blood flow in man. Blake (23) exercised dogs on a treadmill at the rate of 2.5 mph for 40 min and observed no significant changes in C_{PAH} and C_{Cr} . In one of three dogs tested, when "emotional" stimulus was superimposed (a loud horn), C_{PAH} decreased from 161 to 137 ml per min, then returned. C_{Cr} did not change. Greater effects were noted on sodium excretion, which decreased during the emotional response. Carlin *et al.* (50) ran their dogs at 5.6 to 10 mph on a 15° grade for 7 to 20 min; pulse rate was often over 160 per min, and respiratory rate, over 300 per min. Yet there was no change in C_{PAH} or C_{In} , and sodium excretion did not change significantly.

Recumbent human subjects pedaling the equivalent of 0.5 kg weight at 60 cycles per min, which doubled their resting oxygen consumption, showed a 20 per cent reduction in RPF, while GFR remained unchanged, as did E_{PAH} (42). Sodium excretion decreased by 20 per cent. Chapman *et al.* (52) worked their normal male subjects on a treadmill for 16-min periods. The following decreases in C_{PAH} were noted: at 3.0 mph at 0 grade, 6 per cent; 3.0 mph at 5 per cent grade, 17 per cent; at 3.5 mph at 10 per cent grade, 25 per cent below resting control. Work was

continued for another 16-min period, with the following decreases: 15, 27, and 35 per cent, respectively. Recovery was incomplete after 40 min. In a subsequent study (53), the above results were confirmed and, in addition, the work period (3 mph at 5° grade) was prolonged to 3 hours; during the second and third hours, C_{PAH} decreased no more than it had during the first hour (−18.5 to −33.7% below control). Recovery occurred in about an hour. Radigan & Robinson (250) observed that exercise (3 mph on a 5° grade) produced a 42 per cent decrease in RPF, but the C_{In} did not change when the environmental temperature was cool (21 C); when the work was done in a hot environment (50 C), C_{In} decreased by 16.5 per cent, with a 36 per cent decrease in C_{PAH} . In another study, subjects who had run the 440-yard dash at full speed had reductions of 18 to 54 per cent below control in C_{p} , and exhibited also decrease in C_{In} (10). The apparent blood flow remained reduced for 10 to 40 min postexercise.

Harpuder *et al.* (134) compared different grades of work in different postures on C_{PAH} . Light work (3500 kg-m) in the erect or sitting position had no significant effect. At ca. 4800 kg-m, C_{PAH} decreased to $0.85 \pm .08$ of control in the supine, as compared to $0.69 \pm .04$ in the erect position. At 9120 kg-m in the erect posture, the reduction was $0.55 \pm .10$. At the peak of exercise, blood pressure had risen from 114/72 to 164/82 mm Hg, and heart rate from 64 to 142 per min. They point out that with a normal renal blood flow about 1 liter per min (20% of the cardiac output), a saving of 0.5 liter per min is made available for the circulation of active tissues. White & Rolf (339) similarly analyzed the effects of running exercise. With brief maximum exercise, RPF decreased to 20 per cent of control, and under extreme conditions they predicted that almost 1 liter per min of blood was made available or the active tissues.

The cardiac patient shows more marked renal re-

sponses to exercise than the normal subject. A degree of exercise (recumbent) on a bicycle ergometer which had no influence on normal subjects (70 kg-m/min) had the effects shown in table 13 on cardiac patients [Werkö *et al.* (336)]. Patients were grouped into categories based on heart size [Group A, 512 ml/m² BSA; Group B, 796 ml/m² (no right heart failure); Group C, 807 ml per m² (with right heart failure)]. Note particularly reduction in RBF, percentage of cardiac output, and increase in renal vascular resistance. The work of others is in support of this (94, 155, 203). Evidently heart failure lays additional stress on compensatory mechanisms. When exercise is added, more intense neurogenic and hormonal influences serve in shunting blood away from the kidney.

The kidney may not suffer as much as might be anticipated during the curtailment of flow in exercise, at least in heart disease, in view of the findings of Bishop *et al.* (21). They have discovered that the A-V oxygen difference of the kidney of the cardiac patient may increase, during exercise, in apparent contradiction to the generally accepted "flow-limited" characteristic of its circulation. The renal A-V oxygen in 12 cardiac patients (mostly rheumatic heart disease but none in congestive heart failure), averaged 2.03 vol per cent; this increased to a mean of 3.31 vol per cent during exercise. In one, an increase to 12.40 vol per cent was recorded.

Posture and Orthostatic Hypotension

In normal young males, C_{PAH} in the sitting position is $0.91 \pm .04$ of that recorded with the subject supine; in the erect position, it is 0.85 ± 0.14 (242). Tilting of the subject from the horizontal similarly produces reduction in glomerular filtration rate, e.g., 127–120

to 98–93 ml per min (60° tilt), recovering to 126, 117, and 112 ml per min (39).

Motionless standing, or tilting of the subject lying quietly on a tilt-table, leads to progressive venous stagnation, reduced cardiac output, and neurogenic vasoconstriction until the cerebral circulation becomes inadequate, at which point syncope occurs.

When tilting is done in increments from horizontal to 60°, RPF and C_{in} progressively decrease; this is more marked when reflex compensatory mechanisms are good, as manifested by well-sustained blood pressure, than when blood pressure is not sustained and fainting is imminent (36, 60, 72, 286, 334). Patients prone to orthostatic hypotension in particular manifest the latter responses (36). E_{PAH} usually is not altered (36, 334). Filtration fraction tends to increase, suggesting predominantly efferent arteriolar constriction (60, 287).

Two different types of responses are shown in table 14. In table 14 A, compensation was good, and arterial blood pressure was well maintained. In B, in a patient subject to orthostatic hypotension, renal blood flow "opened up" as syncope ensued.

The type of response seen in table 14 B was also shown during fainting produced by cuffing the lower appendages, plus venisection (up to 500 ml) (72). In all cases, when blood pressure fell, C_{PAH} decreased but the calculated renal vascular resistance decreased. Thus, the kidney participates in the more widespread splanchnic vasodilatation which occurs during syncope (14).

It is of interest that the medullary flow increases in the subject (table 14 B) during the failure of vascular compensation. Although this type of calculation of medullary flow must be accepted with some reservation, the data suggest that vascular resistance decreases more markedly in the medullary circulation,

TABLE 13. *Effect of Exercise on Renal Hemodynamics in Cardiac Patients*

| | Brachial BP mm Hg | Cardiac Index | C_{in} ml/min | C_{PAH} ml/min | FF % | RPF ml/min | % Cardiac Output | R dynes-sec cm ⁵ |
|----------------|----------------------|------------------|--------------------|---------------------|---------|---------------|---------------------|--------------------------------|
| <i>Group A</i> | | | | | | | | |
| N=26 C | 90.9 | 3.59 | 108.7 | 404.8 | 27.8 | 731 | 12.2 | 105.6 |
| N=14 E | +6.2 | +0.07 | -2.5 | -48.5 | +3.1 | -90 | -3.4 | +22.9 |
| <i>Group B</i> | | | | | | | | |
| N=7 C | 97.7 | 2.11 | 76.3 | 216.4 | 34.9 | 398 | 10.8 | 183.0 |
| N=7 E | +10.2 | +0.86 | -4.0 | -36.8 | +3.4 | -71 | -3.4 | +24.8 |
| <i>Group C</i> | | | | | | | | |
| N=7 C | 96.3 | 1.94 | 83.0 | 204.6 | 43.3 | 403.6 | 11.2 | 199.7 |
| N=7 E | +5.4 | +0.26 | -8.0 | -23.7 | +2.6 | -48.0 | -1.8 | +65.7 |

[After Werkö *et al.* (336).]

TABLE 14. *Effect of Tilting on Renal Vascular Compensation in Man*

| Position | C_{In} ml/min | C_{PAH} ml/min | RPF ^a ml/min | Medullary ^b Flow ml/min | \bar{P}_A ^c mm Hg | True ^d FF | E_{PAH} | R_K ^e |
|--------------------------------------------------------------|--------------------|---------------------|----------------------------|---------------------------------------|-----------------------------------|----------------------|-----------|--------------------|
| <i>A. Adequate cardiovascular compensation^f</i> | | | | | | | | |
| Horizontal | 141 | 588 | 620 | 32 | 94 | 0.227 | 0.96 | .091 |
| 30 degree | 109 | 543 | 573 | 28 | 116 | 0.190 | 0.88 | .121 |
| 45 degree | 77 | 235 | 262 | 27 | 104 | 0.327 | 0.90 | .238 |
| Horizontal | 152 | 766 | 790 | 24 | 98 | 0.193 | 0.97 | .075 |
| <i>B. Inadequate cardiovascular compensation^g</i> | | | | | | | | |
| Horizontal | 69 | 354 | 514 | 160 | 92 | 0.140 | 0.63 | .108 |
| 15 degree | 62 | 341 | 515 | 174 | 77 | 0.120 | 0.68 | .090 |
| 25 degree | 66 | 358 | 580 | 222 | 57 | 0.110 | 0.59 | .059 |
| 30 degree | 54 | 293 | 425 | 132 | 45 | 0.130 | 0.68 | .064 |

^a RPF = C_{PAH}/E_{PAH} . ^b Medullary flow: RPF - C_{PAH} . ^c \bar{P}_A in Part B calculated from diastolic pressure + $\frac{1}{3}$ pulse pressure. ^d True FF = C_{In}/RPF . ^e Hemat. 40% (assumed); $R_K = (\bar{P}_A - \bar{P}_V)/RBF$, in mm Hg/ml/min. ^f [After Werkö *et al.* (334).] ^g [After Brodwall (36).]

supporting the notion of differential blood flow to cortex and medulla.

Werkö *et al.* (334) found little increase in the renal A-V oxygen difference during tilting, so that renal oxygen consumption tended to decrease. The subject in table 14 *A* showed a decrease from 25 ml per min to 10 ml per min at a 45° tilt, but this was the greatest change in the series. The data thus support the concept of the flow-limited nature of the renal circulation.

Renal Hypoxia and Ischemia

HYPOXIA. Analysis of the response of renal blood flow to hypoxic states has been complicated by the varied techniques and experimental conditions employed, and the varying degrees of hypoxia. Thus, the whole organism may be expected to show a different response than the isolated organ to hypoxia (278). Ischemia presents not only the problem of reduced oxygen supply, but also of accumulation of metabolites in the organ.

Caldwell *et al.* (47) gave to subjects oxygen intakes as low as 9.3 per cent for periods of 5 to 17 min. No consistent effects in C_{PAH} and C_{In} were observed; blood pressure only occasionally showed a slight tendency to increase. Berger *et al.* (15) experimentally reduced arterial oxygen tension from ca. 97 mm Hg to ca. 50 mm Hg in humans. C_{PAH} increased by an average of 13 per cent (-5.2 to +22.8) with no significant change in C_{In} or blood pressure. Acute exposure of dogs to simulated altitudes of 18,000 feet (79.4 mm Hg partial pressure of oxygen) and 24,000 feet (61.6 mm Hg oxygen) caused an increase in renal plasma flow at 18,000 feet, but this generally de-

creased below ground level values at 24,000 feet (193). The seal, when subjected to 10 per cent oxygen or asphyxia, reacts with a significant decrease in RPF and GFR (192), accompanied by marked slowing of the heart and increases in blood pressure. It would appear that mild hypoxic states unaccompanied by systemic reflex vascular alterations manifest a slight renal hyperemia, but more severe hypoxic states or asphyxia trigger vasoconstrictor reflexes in which the kidney participates. Other experimental approaches confirm this. Bing & Knudsen (19) by direct observation of the mouse kidney noted blanching (cortical ischemia) to occur in the range of 6.5 to 10.5 vol per cent oxygen in the inspired air (average 7 vol %), with arterial oxygen tension at 42 per cent of control. It was concluded that a reflex was involved, with centers sensitive to hypoxia in the spinal cord, for it persisted after cord section at T₄, but was lost with renal denervation. It is likely that the medullary centers activated by impulses from the chemoreceptors in the carotid sinus and aortic arch would also participate.

ACUTE RENAL ISCHEMIA. Numerous experiments have been made in which the duration of ischemia has lasted from several minutes to 3 and 4 hours. Short-term occlusion results in rather transient hemodynamic effects, while longer ischemia involves varying degrees of tubular damage which must be taken into account in interpreting clearance data. Short bouts (10-20 min) produce small but variable effects with rapid recovery. No change in blood flow (246), or small decreases (76, 269), or even increases (87) have been reported. Since brief ischemia has been reported to cause reactive hyperemia (262, 293) and when clear-

ances are used a washout "overshoot" could occur (62, 298), some reasons for the variability can be perceived.

Thirty minutes of ischemia (unilateral) in dogs (76) resulted in a fall in C_{PAH} and C_{In} to less than 50 per cent of control, but recovery occurred in 30 min. No significant change in E_{PAH} occurred, indicating continued authenticity of the clearance. Following 45 min of ischemia, C_{PAH} and C_{In} were still much reduced 135 min after release, but now the validity of the clearance could be questioned because of possible tubular damage. Unquestionably, 2 hours of ischemia results in marked and persistent reduction of E_{PAH} (control 0.90–0.94, to 0.11–0.43) (246).

The mechanism of the persistent ischemia is of great interest. One speculation is that prolonged clamping of the artery results in the excessive production and accumulation of pressor substances which act locally (269). Other possible factors should be considered. A locally activated, persisting reflex, either intrarenal (93) or caused by mechanical compression of the arteries and intramural nerve fibers, could be involved. It is noteworthy that renal artery blockade does not have the same effect as venous blockade. Neely & Turner (231) found that renal blood flow in the dog kidney (direct method) after 1 hour of unilateral occlusion of the artery was reduced to 44 per cent of control immediately after release, but was restored to 79 per cent 1 hour later. Venous occlusion for 30 min resulted in a decrease to 58 per cent of control and blood flow remained at this value 1 hour later. Combined occlusion of artery and vein also resulted in poor recovery of flow. With venous occlusion, a persistent weight increase occurred; but with combined artery and vein occlusion the weight was constant, so that congestion of the kidney did not appear to be the answer. The possibility of intravascular thrombosis was raised.

With prolonged ischemia, tubular damage, uremia, and death in renal failure is the outcome. Hamilton *et al.* (128) found that anesthetized dogs with the right kidney previously removed uniformly survived 2 hours of clamping of the left renal artery, and some

survived ischemia of 3 to 4 hours. When the kidney was cooled to 5 to 17 C, percentage survival was improved even with longer periods of ischemia, because of greatly reduced cellular metabolism (20).

The pattern of recovery of renal clearance following 2 hours of clamping of the remaining kidney after unilateral nephrectomy in the dog is nicely shown in the work of Friedman *et al.* [table 15 (97)].

It can be seen that the clearances lose their validity for measuring plasma flow because of tubular damage, revealed by the low E_{PAH} and reduced T_{mPAH} . When plasma flow is estimated by the Fick application, although reduced to less than half of control 3 hours after ischemia, blood flow is fairly well restored in 24 hours. The low C_{Cr} is probably the result of continued back diffusion of creatinine, so that the FF has little meaning for some time after ischemia.

Hypercapnia and Acidosis

Dowds *et al.* (75) studied the effects of progressive hypercapnia in anesthetized dogs rebreathing from a spirometer flushed with pure oxygen to prevent hypoxia. During about 2.5 hours, the carbon dioxide content of the inspired air increased to an average of 16.8 vol per cent (13.5–19.9). This was accompanied by a marked increase in respiratory rate. Arterial blood carbon dioxide increased from 35 vol per cent to an average peak of 52.8 vol per cent. Heart rate slowed and blood pressure declined about 10 per cent below the control. In this range of carbon dioxide increase, C_{PAH} and C_{Cr} did not change remarkably; if anything they decreased with the fall in blood pressure. Brooker *et al.* (37) subjected dogs to 30 per cent carbon dioxide in oxygen for 30-min periods. All dogs became acidotic, with decreased urinary output. Blood flow decreased to an average of 45 per cent of control (25 to 64%). Renal resistance increased from 0.68 to 1.17 mm Hg per ml per min, despite a fall of blood pressure to 93 per cent of control. In similar experiments, Stone *et al.* (296) studied the effects on intact and pharmacologically denervated kidneys of anesthetized dogs. With carbon dioxide inhalation, blood

TABLE 15. *Effects of 2-Hour Renal Ischemia*

| | Control | 3–4 hours | 24 hours | 5–8 days | 2 weeks | 3 months |
|----------------------------|---------|-----------|----------|----------|---------|----------|
| C_{Cr} (ml/min) | 59 | 1.9 | 8.6 | 13.5 | 12.7 | 63.0 |
| C_{PAH} (ml/min) | 182 | 5.2 | 27.9 | 44.7 | 62.5 | 174.0 |
| FF | 0.320 | 0.470 | 0.400 | 0.209 | 0.203 | 0.366 |
| E_{PAH} | 0.66 | 0.048 | 0.142 | 0.263 | 0.327 | 0.84 |
| C_{PAH}/E_{PAH} (ml/min) | 276 | 108 | 196 | 170 | 191 | 208 |
| T_{mPAH} (mg/min) | 13.3 | | 1.4 | 3.17 | 3.23 | 6.0 |

[After Friedman *et al.* (97).]

pH decreased from ca. 7.45 to 7.10. Respiration rate tripled, but blood pressure fell slightly. Renal blood flow showed an average reduction to 24.3 per cent of control (range 11–45%) at the end of the 30-min inhalation period. This was accompanied by oliguria or anuria. Denervation of the kidney apparently prevented the marked decrease in flow observed in the intact kidney and urine production continued. The authors concluded that the increased renal vascular resistance was a reflex component of a more generalized vasoconstrictor response to high carbon dioxide. Franklin *et al.* (93) by the visual "blanching" technique in rabbits inspiring gas mixtures of increased carbon dioxide content (up to 25%) saw blanching (cortical ischemia) when the blood carbon dioxide content had increased to 140 per cent of control. The response was abolished by nerve section, confirming the reflex nature of the phenomenon.

Hypercapnia is an important factor contributing to the marked reduction in renal flow which results during diffusion respiration (297). In this, with respiratory arrest resulting from excess anesthetic action or curare, oxygen is taken into the lungs by the continued removal of the gas from the alveoli by hemoglobin uptake in the pulmonary circulation. Breathing of pure oxygen for 1 hour prior to onset of respiration arrest is essential ("denitrogenation"). Blood content of carbon dioxide rises progressively, since it is not removed by the quiescent lungs. After 30 min of apnea, blood flow had decreased to 28 per cent of the control. Blood pressure had fallen an average of 23 mm Hg during this time and renal resistance increased by 230 per cent. In a denervated series (nerve block), these changes in renal blood flow and resistance were restored to the decreasing control trend. Again, a central origin of the renal ischemia was predicated. Bohr *et al.* (27), although demonstrating a lessened trend for C_{PAH} to decrease in the denervated kidney, nevertheless observed significant decreases (PAH to 38% of control with blood pressure decrease from 116–95 mm Hg). Therefore, circulatory pressor substances must be released in greater amounts to contribute to the vasoconstriction.

It seems reasonable to conclude that the reduction in renal blood flow during hypercapnia and acidosis is centrally mediated. It is nevertheless surprising that in none of these investigations was there recorded an increase in blood pressure. From the reported facts it would appear that the preponderant effect of hypercapnia and the accompanying acidemia was a reflex increase in renal vascular resistance in the face of an actual fall in arterial blood pressure, a con-

comitance of events difficult to reconcile. It may be that anesthesia alters the normal response. Also, it must be kept in mind that the direct peripheral vascular action of carbon dioxide is dilatory (e.g. on vessels of skeletal muscle), which action may become preponderant. This does not preclude the possibility that other tissues, such as the kidney, respond only by constriction.

Hemorrhagic Hypotension and Shock

HEMORRHAGE AND HEMORRHAGIC SHOCK. Acute hemorrhage provokes responses in the renal circulation which are typical of general compensatory mechanisms set into play, viz. reflex vasoconstriction, and shunting of blood to other tissues in order to compensate for low blood flow. In the case of the kidney, if blood loss is great enough, this means shutdown of renal excretory function which, if prolonged, might have serious consequences to the organism. Moreover, a prolonged period of anoxic hypotension will impair the function of the tubular epithelium, adding to the problem of shock the probability of renal failure and uremia.

Following acute hemorrhage, the kidney's circulating autonomy aids in reestablishing flow. Heinemann *et al.* (136) bled anesthetized dogs 1.3 to 3.9 per cent of body weight; blood pressure fell by 5 to 59 mm Hg to levels 91 to 51 per cent of mean control values. Renal blood flow (based on C_{PAH}) decreased more than the blood pressure, signifying vasoconstriction. In four representative experiments, RBF declined from 16.1 (15.6–16.6) to 4.5 (0.3–10.5) ml per kg per min. In three animals, while hypovolemia and hypotension were maintained, blood flow was restored autonomously to 16.5 (11.7–19.5) ml per kg per min in 25 to 70 min. Goodyer & Jaeger (107) found similar responses to moderate hemorrhage in anesthetized dogs, followed by restoration of flow. Denervated kidneys showed a lesser decrease after hemorrhage than the paired intact kidney, but both showed compensatory restoration, indicating that the autonomy is intrinsic. Dibenzylamine selectively injected into one renal artery reduced its responsiveness to hemorrhage compared to the control side (129).

Phillips *et al.* (247) found that rapid, massive hemorrhage in anesthetized dogs was accompanied by almost complete cessation of RBF (C_{PAH}/E_{PAH}). If hemorrhage was not too great, arterial pressure rose as the result of extrarenal vasoconstriction, and renal blood flow was restored but at a figure less than before hemorrhage. In the recovery phase, the kidney ap-

peared to be favored at the expense of the rest of the circulation. The cycle could be repeated with additional hemorrhages. Ultimately, peripheral vasoconstriction failed to maintain an adequate systemic pressure, and renal plasma flow and glomerular filtration fell to low values. It was inferred that at this stage afferent arteriolar vasoconstriction closed the renal circulation in an effort to maintain circulation to vital centers. In view of the possible unreliability of the Fick method (C_{PAH}/E_{PAH}) during hypotension and shock according to Bálint & Fekete (8), this interpretation may not be warranted. The indirect method gave them much lower values than did the direct, giving the erroneous impression of marked increase in renal vascular resistance and marked decrease in the renal fraction of the cardiac output.

Corcoran & Page (62) induced hemorrhagic shock in anesthetized dogs by controlled bleeding to maintain pressure at about 60 mm Hg for 70 min, followed by transfusion. This cycle was repeated two or three times. Clearances (C_D or C_{In}) decreased to zero or nearly so during hypotension. Repeated reduction and restoration of blood pressure led ultimately to a permanent reduction in renal blood flow. Since this phenomenon occurred in dogs with denervated kidneys, it was suggested that the reduced function was the result of appearance in the blood of vasoconstrictor substances. Again, caution must be exercised in interpretation because of the unreliability of indirect methods.

Selkurt (270) noted the persistence of a small flow of blood through the kidneys of anesthetized dogs (direct venous outflow) subjected to hemorrhage of 2 to 5 per cent of body weight to bring blood pressure to consecutive 60 and 40 mm Hg pressure stages, held 90 and 45 min, respectively. Clearances could not be followed because of extreme oliguria and anuria. Renal vascular resistance (calculated from direct flow) was not excessively increased early in the 60 mm Hg pressure stage period [experimental/control = avg. 1.15 (0.73–2.07)], possibly because of operation of renal autonomy. But at the end of the period at 40 mm, the ratio averaged 3.04 (1.53–6.15). Enhanced vasoconstrictor activity as the result of additional hemorrhage, plus increased release of circulating pressor materials, such as catecholamines (325) or serotonin (63), could have accounted for the enhanced vasoconstriction.

On transfusion, renal vascular resistance returned almost to control value, but increased again secondarily as normovolemic shock developed. Terminally, this was as great as 4.7 times the control. Because of

variable degrees of tubular damage, the clearances of PAH and creatinine could not be relied upon for accurate measurement of plasma flow and GFR after transfusion.

TOURNIQUET AND TRAUMATIC SHOCK. Allowing for the time factor and sequences of events, the changes induced in renal function by tourniquet shock in dogs are much the same as observed after hemorrhage. Corcoran *et al.* (63) applied leg tourniquets tight enough to block venous return but not necessarily arterial inflow. RPF and GFR progressively fell until at 90 min they were 25 per cent of control. Blood pressure decreased about 25 per cent, with increased hematocrit ratio. On release of the tourniquet which had been in place for 200 min, blood flow might recover for a time, then decline again if shock ensued. With development of shock E_D , which had remained normal, declined to 0.50. Because flow decreased somewhat, even in the denervated kidney, the vasoconstriction must have been partly of humoral origin. Increased release of serotonin was considered as a possibility. Catecholamine output could have been enhanced.

The effects of tourniquet application and limb crushing in anesthetized dogs was studied by Eggleton *et al.* (80), the tourniquets being left in place for 4 to 5 hours. On release, blood pressure fell and urine flow ceased. With gum acacia infusion to restore pressure, the creatinine clearance still remained about one-third of control. The basis for the reduced creatinine clearance was not satisfactorily explained, but afferent impulses to vasomotor centers, and release of humoral substances which might be vasoconstrictor to the kidney could be considered as possibilities. Back diffusion through damaged tubules did not appear likely under the circumstances of their experiment. Fleming & Bigelow (88) made direct visual observations of cortical blood flow of kidneys with crushing injury to the hind legs. They saw agglutination of the cells in vessels of 20 to 30 μ size as large clumps. In capillaries, the clumps were seen intermittently obstructing the lumen, often causing stasis or even apparent reversal of flow.

TRAUMATIC INJURIES IN MAN. Lauson *et al.* (175) reported renal function studies in shock of varied etiologies in man but mostly resulting from hemorrhage and skeletal trauma. Keeping in mind the limitations of the clearance methods for measurement of blood flow and filtration rate under the unfavorable conditions that apply in shock, general conclusions emerge

which are consonant with the findings in the experimental animal. Filtration rate rapidly declined at a mean arterial pressure of 60 mm, and often ceased entirely between 40 and 50 mm Hg. Estimated blood flow was drastically reduced, and calculated renal resistance was high. The renal fraction of the cardiac output was much below the normal range, but the criticism of Bálint & Fekete (8) must be kept in mind. Despite this, and its autonomy under or during such circumstances, it is tempting to conclude that the renal circulation in man is subordinate to the welfare of the body as a whole.

CONCLUDING REMARKS

The kidney is an organ characterized by a high volume of blood flow resulting in a narrow A-V oxygen difference despite a high rate of oxygen utilization. The A-V oxygen difference tends to remain constant in the face of minor fluctuations in flow, but at very low rates of flow, an increase in the A-V oxy-

gen difference has been observed by several investigators. The remarkable autonomy of the renal circulation may be an adaptation to insure steady delivery of oxygen to the renal tissue.

The constancy of flow appears to be desirable for another reason. The countercurrent system for the concentration and dilution of the urine operates optimally with constant blood flow. When this has been experimentally altered (e.g., increased flow through the medullary circuits) the osmotic stratification in the vasa recta and loop of Henle system has been dissipated, and concentrating power impaired.

Indications are that a countercurrent multiplier system for concentration of serum albumin exists in the vasa recta, a mechanism which would aid interstitial fluid uptake and removal into the systemic circulation. The interesting interrelationship of the vasa recta system to the loop of Henle system in the role of water and salt absorption merits much further study, particularly in the direction of quantitative measurement of regional flow (cortical versus medullary), and the factors which alter it.

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Blood supply to the heart

DONALD E. GREGG
LLOYD C. FISHER

*Department of Cardiorespiratory Diseases, Walter Reed Army Institute
of Research, Walter Reed Army Medical Center, Washington, D. C.*

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FUNCTIONAL ANATOMY

THE HISTORICAL KNOWLEDGE of the heart's integral blood supply parallels knowledge of the broader scope of the cardiovascular system in toto. Thus commencing with Galen's designation of the term "coronary arteries," it nevertheless remained for Harvey (1645) to show accurately that channels existed in the walls of the heart for its own nourishment. Interarterial anastomoses were demonstrated by Lower in 1671 using fluid injection techniques, and in 1704 the ventricular branches of the coronary arteries were visualized by a corrosion technique introduced by Ruysch. Connections between the arteries and the cardiac cavities were shown in 1706 by Vieussens using saffron injections into the coronary arteries, and between the cardiac veins and the cardiac chambers in 1708 by Thebesius using air injected through the coronary sinus. That these cavitary communications were, in fact, different channels was not well documented until the twentieth century when phylogenetic studies by Grant (142), and mammalian studies by Wearn (382) established the existence of intramyocardial trabeculae and sinusoids which separated the veins (Thebesian) from the arterial circuit (arterioluminal), and contributed their own communications (arterio-sinusoidal) to the cavities. The more recent introduction of radiographic techniques (84, 352) for visualization of coronary arteries in intact humans and animals, or in pathologic specimens (18, 37, 338), and of cast-digestion techniques (18, 172, 173, 190-192, 258) for permanent reproduc-

tions of normal and pathologic channels have further advanced and clarified the interarterial and transarterial communications and their branches.¹

The Myocardium

VENTRICLES. Gross dissection studies (108, 153, 232) reveal a rather consistent and orderly arrangement in mammals with quantitative differences overshadowed by qualitative similarities. Every muscle fascicle originates from the fibrous rings at the base, the superficial fibers descending toward and penetrating the apex to form the vortex spirals, and then looping upward as the deeper fibers which ascend along the endocardial surface to reinsert in the annulus fibrosis. Thus, the two ventricles are encompassed by figure-of-eight bands of muscle with origins and insertions at the base and a fulcrum at the apex. The muscular interventricular septum receives part of these fascicles while an intermediate layer encircles only the left ventricle, also adding to the septum.

There are probably no true cleavage planes between isolated fascicles but, rather, the ventricle represents a single muscle mass dividing and branching into intercommunicating fascicles. In any one plane, however, the fibers are more or less constant, the epicardial fibers running perpendicular to the endocardial fibers at any given point.

ATRIA. Nearly all fibers arise and insert into the A-V rings, but some fibers merge and disappear on the muscular coats of the great veins.

Interatrial fibers form the septal areas while the auricles and pectinate regions are largely intra-atrial fascicles. There are two simple layers—an inner horizontal and an outer vertical—bound by much intertwining interdigitation.

CONDUCTING SYSTEM. Commencing with the sino-atrial node at the superior vena cava and right atrium, specialized myomeric conducting tissue traverses the right side of the interatrial septum to the locus of the atrioventricular node (153, 399). The latter is situated on the atrial side of the base of the tricuspid valves' medial leaflet, above the coronary sinus and between

the limbus fossa ovalis and the medial leaflet. From the A-V node, the bundle of His penetrates the fibrous A-V ring and runs in the posterior membranous interventricular septum, branching into the right and left bundles at this site or in the upper muscular septum. The right bundle branch is solitary in its course through the septum to the base of the moderator band, while the left bundle subdivides into many branches. The terminations of each bundle form many fine fasciculi intimately applied to the endocardium before merging with the contractile myocardium.

Coronary Arteries

The course and distribution of the major coronary arteries in all mammalian subgroups is remarkably similar and intergroup differences are less pronounced than intragroup variations. The basic anatomic patterns are thus comparable from the smallest to the largest mammals, i.e., from rodents to whales (63, 78, 142, 298).

There are two coronary arteries, right and left, arising respectively from the right anterior and left anterior aortic sinuses of Valsalva. The ostia are situated above the reflections of the semilunar valves, the right coronary in man being 35° to the right, and the left coronary 65° to the left of the anteroposterior axis of the body (258).

LEFT CORONARY ARTERY. This vessel courses in epicardial areolar tissue anteriorly and to the left in the auriculoventricular groove, between the pulmonary artery and the left auricular appendage, and bifurcates into the anterior descending and circumflex branches (fig. 1). These two branches are quite constant in all species, the bifurcation occurring 1 to 1.5 cm (84, 189–191, 258) from the ostium in man, and 2–4 mm in dogs and smaller mammals (36, 64, 153, 290). In dogs and rabbits, but not in man, monkeys, or higher primates (63, 64, 78, 172, 173, 189, 258), a septal artery arises just prior to, at, or not uncommonly, just beyond the bifurcation on the descendens or circumflex, in that order. Small branches from the left coronary artery are frequently present passing to the pulmonary conus and left atrium, and in the rabbit, branches from both left and right coronary arteries supply the major portion of the vasa vasorum of the pulmonary artery (351). A third primary division has also been described arising between the above and supplying the anterior left ventricle (348).

The anterior descendens follows the anterior interventricular sulcus toward the apex and is of variable length, terminating prior to, at, or beyond the apex.

¹ No attempt has been made to give a complete bibliography which would involve consideration of many thousands of publications. Except for an occasional lead article, the older work is considered by referring to some 40 to 50 reviews, monographs, and symposia. Direct but incomplete reference is made to the more recent work not covered in such summaries. By this means, most of the important work in the field can be found by the interested reader although direct reference may not be made to it.

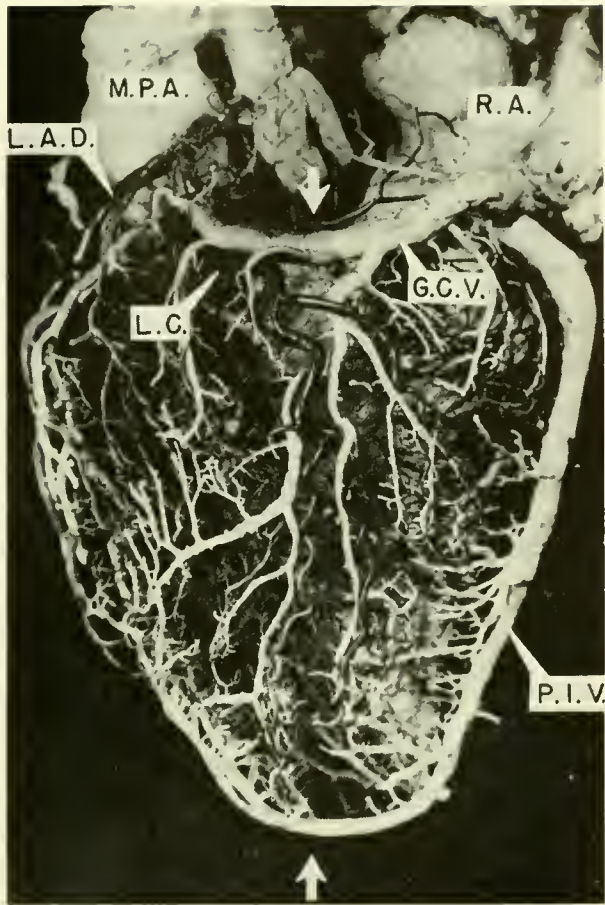


FIG. 1. Vinylite cast of a human heart. Anterolateral aspect of left ventricle following digestion of muscle. *M.P.A.* = main pulmonary artery; *R.A.* = right atrium; *L.A.D.* = left anterior descending coronary artery; *L.C.* = left circumflex coronary artery; *G.C.V.* = great cardiac vein; *P.I.V.* = posterior interventricular vein. [From James (191).]

In humans it terminates 40 per cent of the time at the apex, and in 60 per cent, ascends 2 cm or more in the posterior longitudinal sulcus, while in rabbits it rarely reaches the apex (64, 84, 153, 191, 258). It is covered by bridges of ventricular myocardium for most of its course (292). There are from two to seven ventricular branches, the large left ventricular branches coursing over the anterior surface toward the apex, the small right ventricular branches crossing the interventricular groove to supply a narrow band of muscle and to anastomose with right coronary branches. Anastomoses exist with anterior ventricular branches of the left circumflex coronary artery and at the apex, with the latter's marginal branch and the posterior descending artery whether of circumflex or right coronary origin (18, 189, 191, 258, 337). Septal branches penetrate deeply from the underside of the vessel all along its course in the anterior sulcus.

In humans, primates, and pigs, these branches are not supported as in dogs and rabbits by an individual septal artery arising from the main left coronary or origin of the descendens. A fairly constant branch to the pulmonary conus region exists in most species.

The left circumflex follows the auriculoventricular groove to the left, coursing under the left auricular appendage and terminating at a variable distance from the posterior longitudinal sulcus. It is largely an epicardial vessel, surrounded by areolar and adipose tissue, and rarely covered by muscular loops (292). In dogs it almost always reaches or crosses the crux of the posterior sulcus, terminating as the posterior descending artery, whereas in pigs (64, 289) it rarely does so. In man, higher primates, and rabbits, the vessel usually ends at the obtuse margin (63, 78, 191, 258). An average of three anterior ventricular branches and three atrial branches occurs in man and dogs (36, 64), the former coursing to the apex to anastomose with the anterior descendens branches. Posteriorly, communications exist with the right coronary either from the posterior descendens or the marginal branches. In the dog a branch of the left circumflex at the posterior crux passes deep to supply the A-V node and His bundle (172, 173).

RIGHT CORONARY ARTERY. The main right coronary artery arises from a single ostium in its aortic cusp, but not infrequently, especially in dogs and primates, smaller ostia of accessory branches are also present (63, 258, 290). The right coronary passes anteriorly behind the pulmonary artery and follows the respective auriculoventricular groove to the right (acute) margin of the heart. In dogs and rabbits it usually terminates here as the marginal branch, whereas in pigs and man it invariably (93%) reaches the posterior crux to become the posterior descending artery (64, 191, 289). In its course it gives off an average of three atrial branches, one of which, the dorsal (posterior) right atrial artery, is the major supply to the S-A node in man and dog (172, 190), and three to five right ventricular branches. Posteriorly, in man and pigs, a branch to the A-V node is given off at the crux, corresponding to the branch from the circumflex in dogs (172, 189, 190, 246, 258, 399). A constant branch to the pulmonary conus frequently arises from an accessory ostium.

Although it is evident that the course and distribution of the coronary arteries is basically similar in the various species mentioned, the ramifications are such as to permit a breakdown into patterns of dominance. Thus, in all species, the entire anterior and lateral left ventricle is supplied by the left coronary branches,

and the free right ventricular wall by the right coronary artery. The most variable area is posterior, and it is by virtue of the communication of the posterior descending artery with either the left or right coronary artery, or both, that the designation "dominant" pattern has arisen (18, 37, 84, 153, 258, 348). Hence, dogs are universally left coronary dominant, the left circumflex branches supplying the posterior left and right ventricles, the posterior septum and A-V node. This pattern is the least common in man and pigs, approximating 20 per cent of cases in the former. Pigs are generally right coronary dominant, while man, both living and autopsied, and the higher primates manifest this pattern half of the time and a balanced circuit in approximately a third (37, 63, 84, 153, 348). In the perfused human heart, however, this pattern of dominance is not found (370).

The secondary divisions of the major coronary branches in man are consistently different over the two ventricles, the branches of the anterior descendens and left circumflex arising at acute angles and coursing to the apex, while those of the right coronary arise at right angles and course toward the anterior interventricular sulcus (191). The terminal branches are likewise different; those over the left ventricle are perpendicular to the epicardial course, while those over the right ventricle are parallel. Once the arteries penetrate the myocardium, they lose their tortuosity and linearly follow the muscular grain in a plane between the superficial and deep muscle layers (153, 191, 258).

The functional supply to the conducting tissue bears further comment since it has been shown in man and dogs that mortality and morbidity are increased when ligation of vessels includes septal and nodal arteries (5, 61, 246). Of the three atrial branches from each coronary artery, the crista branch of the dorsal right atrial artery is the major supply to the S-A node in man (60–70%) and dogs; rich anastomoses exist with the ventral left atrial artery in 75 per cent of dogs whereas, in man, this latter vessel is the major supply to the S-A node in 40 per cent (153, 172, 173, 189, 190, 399). In rats and dogs (172, 174), and possibly in man, anastomoses with extracardiac vessels are readily shown at the junction of the superior vena cava and right atrium. Rats have a dual blood supply to the heart, the atrial and S-A nodal vessels stemming from cardiaco-mediastinal branches of the internal mammary and subclavian arteries, while the ventricles, A-V node, and parts of the atria are supplied by the coronary arteries.

Recent vinylite cast techniques have shown a consistent artery to the region of the A-V node arising,

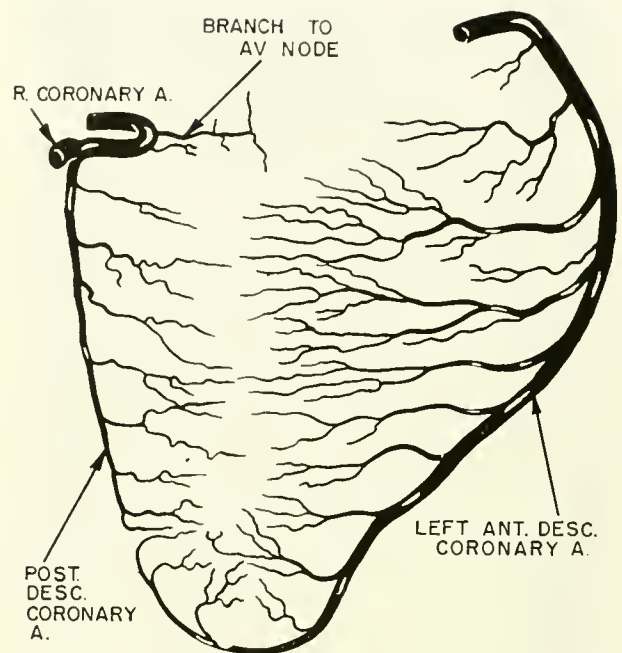


FIG. 2. Drawing of the blood supply of the normal human interventricular septum. Note the preponderance of supply by the left anterior descending coronary artery and the U-turn of the posterior right coronary artery which gives off the branch to the atrioventricular node. [From James (189).]

in man, from that coronary artery which crosses the posterior crux (189–191, 246). Thus, in 80 per cent, this was the right coronary, the left in 10 per cent, and from both in another 10 per cent. In 100 per cent of a large series in dogs (246), a similar vessel arose at the crux from the left circumflex coronary. This vessel, variously named the posterior septal artery and ramus septi fibrosi, courses along the base of the interatrial septum and penetrates the annulus fibrosus to supply the His bundle and upper interventricular septum (246, 399) (fig. 2). In its course it freely anastomoses with atrial vessels, predominantly the dorsal left atrial artery and, from below, the anterior septal arteries.

The interventricular septum receives its blood supply from the anterior septal artery and penetrating branches of the anterior and posterior descending arteries (36, 172, 173, 189, 190, 246, 258). The former is well developed in dogs but in man and higher primates it is somewhat vestigial, although easily identified as the first and largest branch of the anterior descendens.

The anterior branches in man are 40 to 80 mm in length, supply the anterior two-thirds to three-fourths of the septum, and penetrate near the right ventricular side remaining under the right ventricular endocardium before terminating deeper in the septum.

The posterior branches are shorter, up to 15 mm; they supply the posterior one-third of the septum and anastomose with the anterior branches. In dogs, however, the anastomoses are deficient and the large anterior septal artery's superior and inferior divisions supply the central portion of the upper two-thirds of the septum including the moderator band and lower His bundle (36, 64, 246, 290, 399). The more distal bundle branches are supplied by the penetrating vessels.

CORONARY BLOOD VOLUME. Available information regarding coronary blood volume (artery through coronary vein content) is incomplete and quite approximate. In humans, at postmortem, average values in both sexes range from about 2 to 6 ml per 100 g heart weight (310). In the arrested dog and cat heart and isolated beating dog heart, values approximate 6 to 8 ml per 100 g heart muscle (129).

Myocardial Arterioles and Capillaries

As the superficial arteries penetrate the myocardium, they bifurcate or trifurcate disproportionately so that the parent vessel and diameter grow gradually smaller while the daughter vessels narrow rapidly, terminating in the capillary network (294, 295). The deeper arterioles lose the internal elastic membrane and subendothelium present in the more superficial layers and contain a single layered intima and a media one to two muscle layers thick. As the arteriole narrows, its muscularis becomes discontinuous and the muscle cells decrease in frequency with increasing distance from the arteriole. This latter vessel, the metarteriole, is continuous at its distal end with the simple endothelial tube characterizing the capillary. A group of one or more, usually three, muscle cells at the proximal end of a capillary constitutes a sphincter and denotes the precapillary.

Recent studies have suggested that the myocardial capillaries are not all functional at all times as was previously believed (294, 295). It has been shown that the metarterioles and precapillary sphincters can close off the capillary lumen. Thus, during sphincteric contractions, the nucleus of the endothelial cell underlying the sphincter becomes rounded and is forced into the lumen of the vessel thereby occluding it. During relaxation and in those regions where there are no sphincters, the nucleus is flattened along the wall and the lumen is open. The demonstration of nerve fibers accompanying the vessels in the areolar connective tissue and terminally "splaying" to surround the myocardial cells and sphincters, and the absence of

any such supply to "true" capillaries, lends support to a changing dynamic state of capillary patency and function. Moreover, the demonstration of anastomotic connections between arterioles, metarterioles, precapillaries, and venules in both man and dogs suggests arteriovenous shunting as an integral component of the myocardial capillary circulation.

In the newborn human and rabbit there is approximately one myocardial capillary per four myocardial fibers, corresponding to 4,000 capillaries per mm² of tissue (382). In the human adult the ratio of capillaries to fibers approaches 1:1, while the capillary concentration approximates 3,000 to 4,000 per mm² of tissue, both values being fairly constant over a wide age span (6, 125, 382). The capillary diffusing area per cm³ of tissue averages 1,145 cm² in children, and 1,184 cm² in adults (6). An analysis of tissue from various ventricular areas reveals similar capillary densities and surface areas for the human left ventricle, right ventricle, and papillary muscle, whereas the interventricular septum shows a decrease in both these parameters. While the maximum diffusing distance is calculated to be 8 μ in all of the above areas, that to the conducting system proper is appreciably greater.

In contrast to the septal myocardium, there is a scanty capillary supply to the A-V node and His bundle in sheep and cattle (125). Capillaries and conducting fibers are not intimately connected and are often separated by wide spaces of connective tissue. In the His bundle, capillaries are located outside the dense band of fibers with the central nuclei far from the source of blood. Other investigations in dogs and humans have shown a well-developed system of sinusoids anastomosing with capillaries, veins, and arteries which traverse the annulus fibrosus and supply the A-V node and common bundle (365, 366).

Exchange of metabolites in myocardial capillaries has received anatomic amplification and clarification by electron microscopic techniques (111, 270, 286). The endothelial cells form a continuous capillary and arteriolar lining without any evidence of intercellular or intracellular pores. Many vesicles or caveolae are concentrated under the cell membranes facing both the capillary lumen and pericapillary spaces, and are believed to represent continuous invagination and pinching off of the plasma membrane which then crosses the cell and liberates nutrients, metabolites, and other materials (111, 270, 286). Injected colloidal gold particles have been photographed concentrating along the luminal side, engulfed and transported across the cell in vesicles, and finally, phagocytized by macrophages in the pericapillary spaces. This transport mechanism has been variously termed "pino-

cytosis" (286) and "cytopempsis" (270), the latter being preferred since it does not imply actual utilization of the transported substances by the endothelial cell.

Myocardial Veins

There are twice the number of venous as arterial channels in the heart, their density in the left ventricle greatly exceeding that of the right (191), and they have been subdivided into superficial and deep circuits (153, 365, 366). The superficial left ventricular veins parallel the arterial branches and course toward the base of the heart to empty into the great cardiac vein anteriorly, and its continuation in the left auriculoventricular groove, the coronary sinus, posteriorly. The latter empties into the right atrium in the posterior-inferior interatrial septum located between the medial end of the inferior vena cava and A-V ring, and receives subsidiary trunks up to its orifice (183). The anterior cardiac veins drain the right ventricle and are smaller, frequently solitary, trunks which empty individually into the right atrium just above the A-V valves (153).

The deeper venous circuit has communications with both atrial and ventricular cavities via Thebesian and sinusoidal channels (153). Myocardial sinusoids or trabeculae are especially rich in the ventricular walls and maintain communications with arterioles, capillaries, venules, and the heart cavities (64, 153, 189, 191, 365, 366). These sinusoids are lined by a single layer of endothelium and range from 40 to 75 μ in dogs, and 60 to 90 μ in newborn humans in the septal myocardium. In dogs and pigs there is a massive formation of sinusoids in the left ventricular wall communicating with the cavity (64).

Collateral Circulation

As noted earlier (*vide supra*), intercoronary anastomoses were first demonstrated by Lower using a watery injection of dye, and in 1803 von Haller reported on the extracardiac communications of the coronary arteries, utilizing the same techniques (153, 382). The latter were principally channels from the base of the pulmonary artery and veins, root of the aorta and venae cavae, and other basal (usually atrial) vessels, to vessels in the intrapericardial reflections. These vessels are largely from the internal mammary artery via the pericardiophrenic branch, but communications also exist with the bronchial arteries.

In lower vertebrates the blood supply to the heart

is nearly all extracardiac in origin, whereas the rat maintains a dual supply of both intracardiac and extracardiac origin. In normal mammalian hearts the extracardiac communications are of the order of small arterioles and capillaries and are anatomically and physiologically insignificant.

Intracardiac coronary anastomoses in human hearts and those of various laboratory animals have been the subject of numerous pathologic and experimental investigations during the past decade. Collateral arterial communications in normal hearts have been anatomically divided into those stemming from the same major coronary artery, i.e., intracoronary, and those between the right and left coronary branches, i.e., intercoronary (18, 258). All mammalian species show some intercoronary anastomoses, especially over the anterior left ventricle, while intercoronary anastomoses vary appreciably between species, the dog's being fairly well developed, the pig's poorly, and man's quite variable; the greater proportion occurring in the muscular interventricular septum (18, 189).

Functional collateral channels, as opposed to anatomic communications, have been defined for mammalian hearts as those above 40 μ in diameter, i.e., those which do not traverse a capillary bed (37, 38, 338). High viscosity fluids do not penetrate vessels below 40 μ and, utilizing this technique or those with graduate spheres above 35 μ , 6 to 9 per cent of normal human hearts have adequate collateral channels (38, 291, 411). Conversely, latex casts have shown luxuriant anastomoses ranging from 20 to 350 μ in all normal hearts and in all myocardial areas below the subepicardial layer of muscle (18). Thus, while the experimental and pathophysiological approaches to this problem will be more fully discussed in a later section, the disparity between the functional state, i.e., its physiologic competency, and the nonfunctional state, i.e., its anatomic patency, becomes more obvious and the reason for the designation of the coronary arteries as "end arteries" more apparent (153, 404).

While the above discussion has dealt mainly with arterial collaterals, venous collateral channels freely communicate over the surface of the heart (153), including those between the anterior cardiac veins of the right ventricle and the left ventricular coronary sinus system. Extracardiac communications of the cardiac veins are not uncommon especially in lower mammals, and are usually related to the persistence of the left caval or cardinal veins. In the pig, large communications may exist between the hemizygous vein and the great cardiac vein, the latter also having substantial epicardial connections with the anterior

cardiac veins (64). Of greater concern, however, is the existence of communications between the ventricular cavities and the trabecular sinusoids via the Thebesian, arterioluminal, and arteriosinusoidal vessels (153). Although dyes and particulate matter have been recovered from ventricular myocardium following intracavity injections (153), this has only occurred experimentally with *a*) high ventricular end-diastolic perfusion pressures, *b*) congenital aortic and pulmonic valvular atresia with intact septa, and *c*) in the arrested heart or one in which the heart stopped before its removal. As a result of simple pressure differentials, the dye or particle moves into the myocardium, while for the same dynamic reasons only the reverse could, and indeed does, occur in the actively beating heart (153, 404).

Congenital Anomalies

Variations in the course and number of nutrient vessels to the myocardium are not uncommon and, as with other organ systems, are usually of no physiologic concern. However, the acceptance of the clinical syndrome of the aberrant left coronary artery as part of a group of congenital coronary arteriovenous fistulae, and its recent physiologic documentation, has prompted this brief digression into those embryologic and phylogenetic ramifications relating to the coronary arteries.

The lowest orders of vertebrate hearts have no well-defined myocardial blood supply. Thus, the single-chambered ventricle of the lamprey nourishes its myocardium via extensive intramyocardial sinusoids in direct communication with the ventricular cavity (142). The arterial supply to vertebrate orders below reptiles arises from cranial and caudal vessels coursing through the cardiac ligaments. Reptilia maintain a single cranial supply of vessels which are related to the fishes' epibranchial and hypobranchial vessels, the latter disappearing and moving caudally with the loss of the gills (8).

Mammalian coronary arteries arise from primordial buds in the truncus arteriosus during the 5th week of gestation. At this time, the endocardial cushions and longitudinal ridges are also forming, respectively dividing the heart and truncus into two channels. The heart has been actively beating and forcing blood through the systemic circulation since the 3d week, and the heart itself is nourished by the sinusoidoluminal channels (8, 101, 140). In the fetal rabbit, endothelial-lined trabecular spaces spiral toward the surface forming capillaries and epicardial vessels. The

latter join with venous cords growing caudally in the epicardium from the sinus venosus to form the first of the myocardial vessels. Arterial buds form a few days later and spread as a solid column of cells to the bulbus cordis, with subsequent extensions and branches to the lateral areas. As these epicardial arteries enlarge, the sinusoids decrease in size by a condensation and compression of the myocardial cortex, finally becoming capillaries (140). In lampreys and lower fishes, and in certain human congenital anomalies, this condensation does not occur, the spongy trabecular network remaining undisturbed (141, 382). In higher fishes and mammalia there is an outer, condensed, capillary-containing layer supplied by epicardial vessels, and an inner trabecular layer with retained cavitory communications. Thus, the variations in the number and site of the coronary ostial anlagen will determine the final origin of the coronary arteries, while variations in the epicardial course and degree of myocardial condensation may determine the eventual communications. These anomalies have recently been presented as follows (101).

a) Coronary arteries arising from the aorta and supplying the heart in normal, albeit variable, fashion without abnormal communications. This includes those with single ostia and single coronary arteries, common sinus, accessory ostia, and ostia elsewhere in the aorta. In a recent large series, such anomalies occurred in 52 cases of 18,950 autopsies for an incidence of 2.75 per 1,000 (4). Reviews of single coronary arteries in man have stressed the absence of clinical symptoms except those related to associated cardiovascular anomalies (4, 308, 350). However, the anomalous distribution seems to predispose to early sclerotic changes and myocardial infarction, the average age of death in adults being 45 years. In one series (308), all cases of myocardial infarction, fibrosis, or ischemia were related to the absence of a left coronary artery, i.e., the presence of a single right coronary artery.

b) Coronary arteries supplying blood to grossly abnormal hearts in which congenital pulmonary or aortic atresia exists in conjunction with intact ventricular septa and intact A-V valves. Ventricular blood is forced from the cavities via myocardial sinusoids which anastomose in the epicardium with the coronary arteries. This type, fortunately, is rare.

c) Coronary arteries distributing blood abnormally. These may be via left-to-right arteriovenous shunts into the right heart chambers, cardiac veins, or pulmonary artery, or via arterioluminal shunts into the left heart chambers (fig. 3).

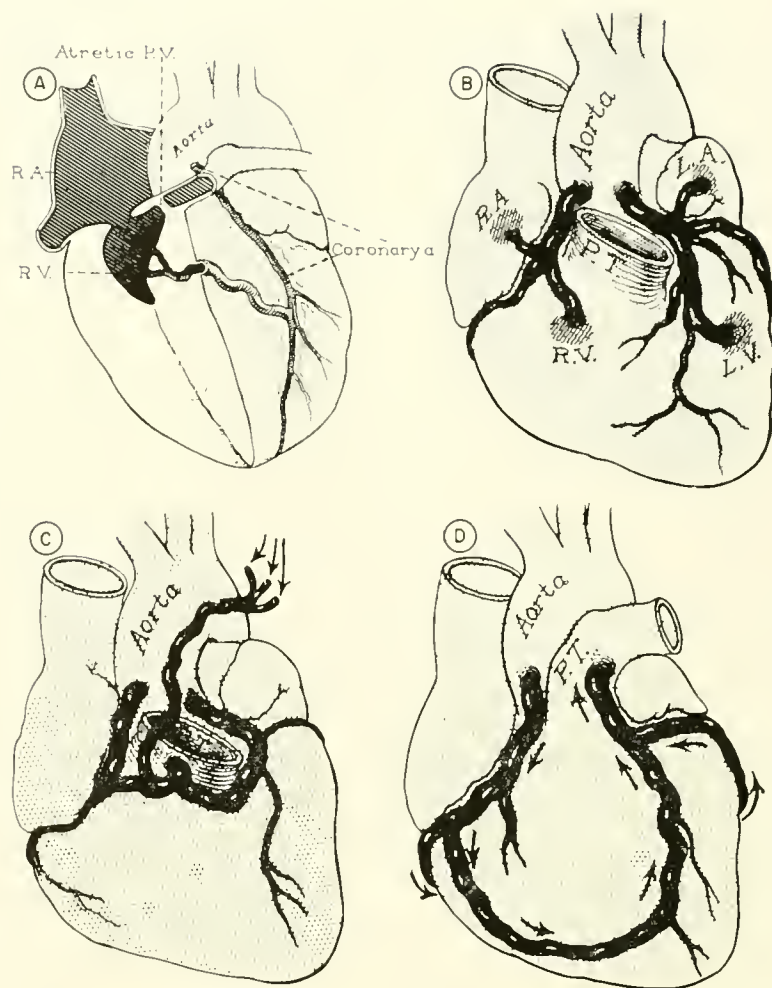


FIG. 3. Anomalous coronary artery communications: *A*: retrograde flow from right ventricular cavity to epicardial coronary arteries via myocardial sinusoids in presence of pulmonic (or aortic) atresia with intact ventricular septum and competent auriculoventricular valves. *B*: composite illustration of aortic communication with the cardiac chambers via the coronary arteries. *C*: communication of the aorta with the pulmonary artery via aberrantly coursing coronary arteries. *D*: anomalous origin of the left coronary artery from the pulmonary artery. [From Edwards (101).]

Congenital coronary arteriovenous fistulae have been demonstrated in humans at thoracotomy, or preoperatively utilizing angiocardiology and coronary arteriography (104, 356). While gasometric analyses may suggest a left-to-right shunt similar to septal defects or a patent ductus arteriosus, auscultatory findings have more often suggested the latter. Clinical symptoms and signs, present in half the cases, reflect a high output congestive failure, the shunts averaging 40 per cent of the cardiac output (356). The embryologic defect is probably a persistence of myocardial sinusoids although the large, sometimes aneurysmal, dilatation and veinlike thinning of the arterial wall is a "common feature to all arteries proximal to an arteriovenous shunt," and may, therefore, be a secondary rather than a primary alteration (101). A recent review now totals 71 cases (104).

The anomalous left coronary artery has recently become a subject of increasing clinical and physio-

logic interest, not only because it is the most common of the congenital coronary artery aberrations and readily diagnosed with modern clinical techniques, but also because of the controversy concerning the direction of blood flow in the aberrant vessel. There have been over 60 cases reported in various reviews on this anomaly, approximately one-fourth occurring in adults in whom an apparent attenuation of the pathophysiologic process is manifested. As the truncus is dividing into aorta and pulmonary artery (5th week of gestation), the primordial coronary ostial buds have already been established and the growth of solid arterial cords has commenced (8, 69) (fig. 4). The predominant finding of normal and equal-sized aortae and pulmonary arteries strongly implicates a malposition anteriorly of the left coronary artery as the primary developmental defect, but the occurrence of hypoplastic aortae, in rare cases, does not negate the possibility of an abnormal division of the truncus arteriosus.

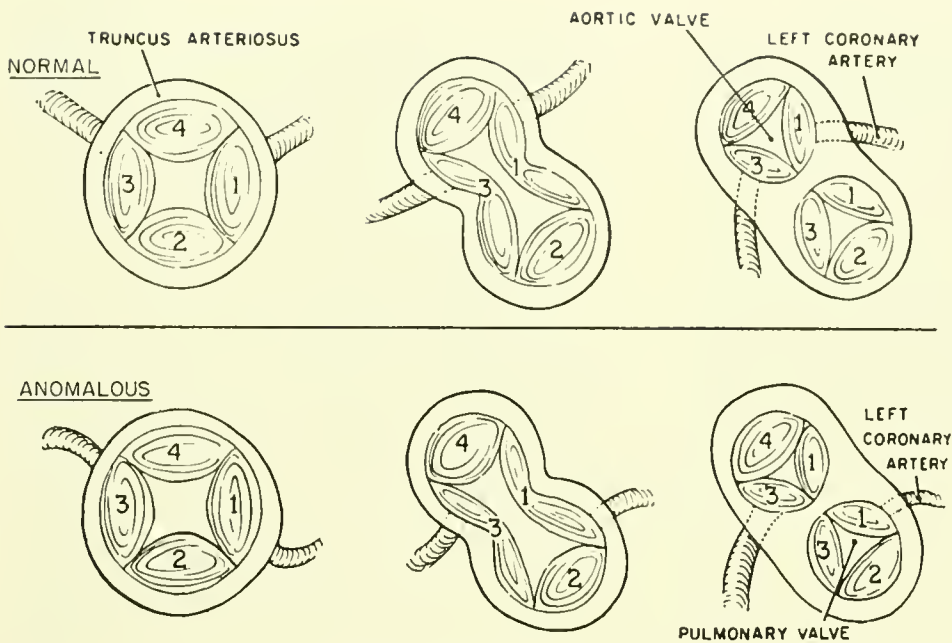


FIG. 4. Diagrammatic representation of the normal and the anomalous origin of the left coronary artery following torsion and division of the truncus into aorta and pulmonary artery. [From George & Knowlan (127).]

The anatomic abnormality was first described for an aberrant right coronary artery in 1886 (101). At that time, the suggestion of reversal of flow in the aberrant vessel was postulated because of the tortuous, dilated nature of the arteries involved and a simple reflection on the pressure differential between the two circuits. The anatomic aberration of the left coronary was described in 1911 and the clinical syndrome of infarcts in 1933 (101). Electrocardiograph findings suggest a recent anterior or anterolateral myocardial infarction (58, 69, 101, 127, 210), while angiocardiology or cine-angiocardiology reveals a normal right ventricle and pulmonary artery and a dilated, thinned left ventricle without evidence of filling of the left coronary artery from the pulmonary artery; retrograde aortography reveals a dilated right coronary and late filling of the left coronary (from right coronary collaterals). The aberrant artery in both adults and infants is a thin-walled veinlike vessel with an atrophied media. Grossly visible right-to-left coronary anastomoses were present in 27 per cent of the adult specimens.

Using pathologic specimens and surgical observations, but without definitive physiologic data for support, Edwards earlier proposed a hypothesis sustaining the concept of retrograde flow and refuting that of antegrade flow from the pulmonary artery (101). Physiologic proof of the retrograde nature of

flow in the aberrant left coronary has been presented at thoracotomy in a preoperatively diagnosed 2½-month-old child (325). Prior to ligation of the vessel at its origin from the pulmonary artery, the pressure in the left coronary artery was 30/15 mm Hg, rising to 75 mm Hg systolic distally after occlusion, while a simultaneous pulmonary artery mean pressure was 25 mm Hg. Arterial saturations in the corresponding vessels were 100 and 76 per cent, respectively. A post-ligation rise of 30 mm Hg systolic pressure, and a decreased paradoxical bulge of the left ventricular infarct area, as blood now traversed rather than shunted away from the myocardial bed, lends final support to the retrograde flow thesis. In contrast to the invariably fatal outcome within the first year of life, this patient is alive and asymptomatic.

The Cardiac Nerves

The nerve supply to the heart is mediated through the cardiac plexuses located above the base and between the aortic arch and tracheal bifurcation (397). Vagal, sympathetic, and dorsal root fibers intermingle and tend to lose their identity as they decussate into right and left halves before entering the pericardium. Functionally, however, they are best divided into sensory and autonomic functions.

The sensory afferent fibers originate in thoracic

dorsal ganglia. They are largely unmyelinated in their myocardial course (153, 397), and supply the pain-sensitive areas in the pericardium, connective tissue, adventitia, and walls of the heart, terminating as fine beaded nerve fibers and loops similar to those in the skin and skeletal muscle. Sensory axons traveling in sympathetic plexuses and through the lower two cervical and upper four thoracic sympathetic ganglia complete the afferent limb of the pain reflex. In both man and dog, ablation of the stellate and upper four thoracic ganglia, or upper four dorsal thoracic spinal roots, completely blocks the pain pathway (397). These neurons send fibers via the posterior spinal roots which synapse in the posterior spinal horn with secondary fibers running in the spinothalamic tracts and terminating in the posterior-ventral nucleus of the thalamus (fig. 5). While connections to the cortical somatic sensory areas exist, these only modify the reaction to, rather than the perception of, cardiac pain.

The autonomic innervation includes both an af-

ferent and efferent vagal and sympathetic supply. Vagal parasympathetics are mediated by the cardiac plexus and stem from both right and left vagi and the recurrent laryngeal nerves. A large portion of both afferent and efferent fibers is distributed to the great vessels superior to the heart, while the greatest part of the remainder supply the interatrial septum and the sino-atrial and A-V nodal areas (12, 76, 153, 368, 397). The large number of fibers in the latter areas contrasts with the paucity of fibers supplied to the atrial muscles via atrial arteries and the even smaller number found in the ventricles. Using veratrum alkaloids, only the left coronary artery system, i.e., the left ventricle, has been found to contain afferent vagal ganglia which contribute to the Bezold-Jarisch reflex while, conversely, no efferent vagal supply is present in either ventricle (12, 76, 368). The sympathetic efferent discharge is largely to ventricular muscle and coronary arteries and contains both cardiomotor and vasomotor fibers, while atrial efferents are predominantly to the S-A node and are cardio-accelera-

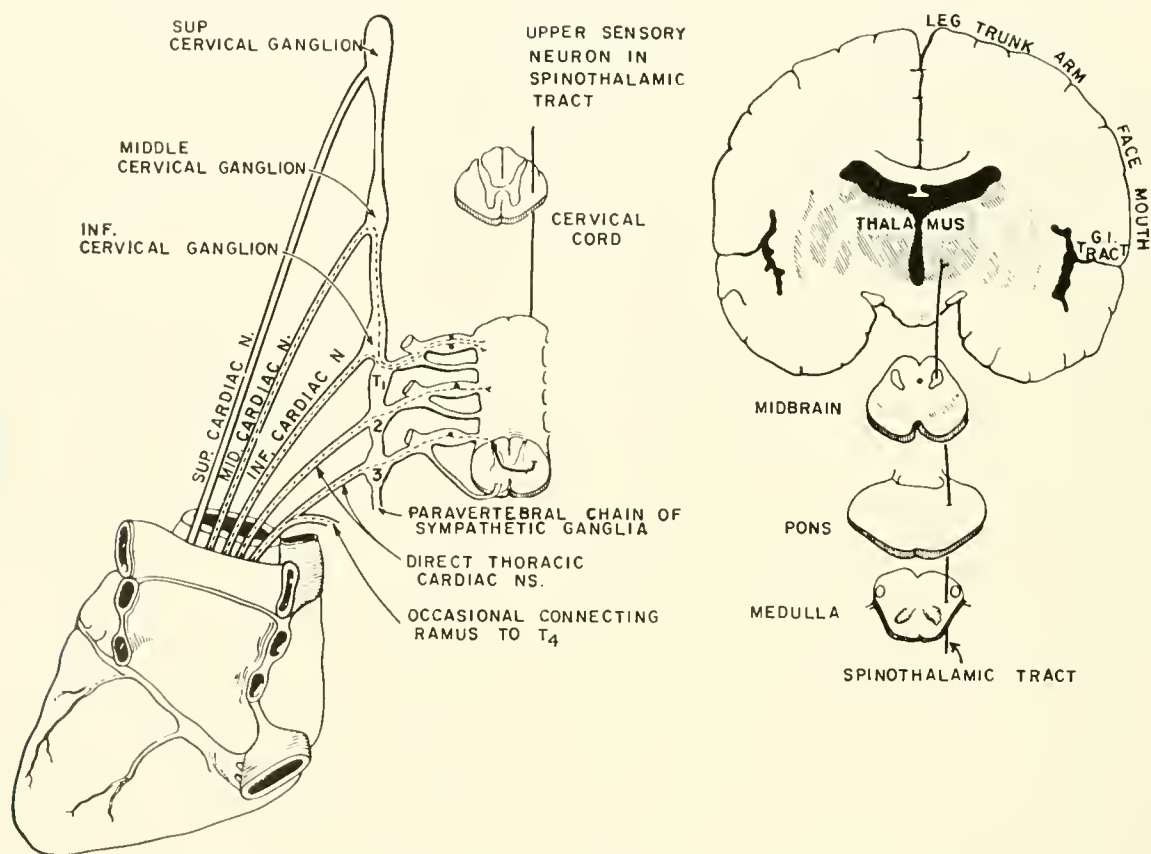


FIG. 5. Illustration of the cardiac nerves and their central communications. Parasympathetic efferent and afferent fibers from the vagus and recurrent nerves join the cardiac plexuses at the base of the heart. [From White (397).]

tor. Since staining techniques have been notably poor in differentiating vagal and sympathetic terminals, most of the available functional neural anatomy stems from physiologic and pharmacologic observations (12, 76).

Lymphatic Drainage of the Heart

The myocardial lymphatics arise at the periphery of the capillaries and drain into deep and superficial lymphatic plexuses. They lie, respectively, immediately subjacent to the endocardium and epicardium, the former draining toward the surface to join in the formation of lymphatic trunks. The vessels course in the anterior and posterior longitudinal sulci and condense to form left and right common trunks. The left trunk passes between the pulmonary artery and left atrium, and the right behind the pulmonary artery, both terminating in the "cardiac lymph node." This node is well delineated in the dog and is regularly found between the innominate artery and superior vena cava (86, 287).

Recent studies have indicated a pathologic similarity between experimentally induced myocardial fibrosis secondary to chronic obstruction of the common lymph trunks and idiopathic endocardial fibroelastosis or endomyocardial fibrosis (261).

PREPARATIONS AND METHODOLOGIES OF SPECIAL INTEREST IN THE STUDY OF THE HEART AND ITS CORONARY CIRCULATION

Many of the various preparations, procedures, and instruments have been considered in previous reviews (7, 10, 136, 146, 149, 152, 153, 299, 384, 400).

Preparations

The coronary circulation has been studied with the heart in various degrees of deviation from the normal state. These preparations include the heart-lung, the isolated heart, and the open or closed-chest animal or human with anesthesia. The use of the nonworking isolated perfused heart by Langendorff in 1895 (221) and by Porter (293), in which arterial inflow and venous outflow could be measured, laid the groundwork for our understanding of the coronary circulation. An early bottleneck to the study of the coronary circulation in the isolated heart was the lack of an efficient means of oxygenating the blood. The isolation of the heart connected to its lungs (215), and subse-

quent use of this preparation by many others (10) contributed extensively to our knowledge of the heart and coronary circulation. There are many variations of this procedure but, in general, the heart and lungs are removed in such a way that the cerebral circulation and the vagal and sympathetic nerves remain connected to the heart while the venous return, cardiac output, ventricular volume, heart rate, aortic and pulmonary resistances, atrial, ventricular and arterial pressures, and the chemical composition of the blood can be separately altered and controlled and even cardiac biopsies made. Early in its use, Morawitz & Zahn (272) developed a cannula for insertion into the coronary sinus via the right atrium. The flow through it was presumed to quantitate total venous return from the vessels of the heart. Although this idea was later shown not to be true, the investigation was important for it enabled the experimenter to study the coronary sinus fraction of coronary venous outflow not only in the isolated heart but also in the heart beating in situ. An artificial lung was substituted by Evans *et al.* in 1934 (107), and since then the development of such devices and preparations has been rapid, permitting total coronary venous flow measurement and fractionation of coronary sinus drainage and noncoronary sinus drainage in the working and nonworking isolated heart. Some of the better arrangements are as follows: *a*) Coronary venous drainage is pumped through an oxygenator into the coronary arteries. *b*) The heart is isolated in a manner similar to the classical heart-lung preparation except that instead of returning the blood to the right atrium and through the lungs to the left atrium, the left ventricle usually discharges its blood through a resistance into a reservoir from which it returns to the left atrium. This is a closed system except for the escape of blood through the coronary vessels into the right heart which receives no other blood (335). This coronary venous blood may be ejected through the pulmonary artery and collected, or it can be separated into coronary sinus and non-coronary sinus fractions by coronary sinus cannulation. In either case the blood goes into the venous system of a donor dog whose arterial system is connected to the reservoir. *c*) The isolated beating heart doing no external work but with its nerves and cerebral circulation intact may be studied within the chest of dog (or man) by directing systemic venous return through a pump oxygenator into the aorta, thus bypassing the heart. Total coronary venous drainage can be measured in the pulmonary artery or it can be fractionated by also collecting separately coronary sinus flow. The effect of systolic and diastolic ventricu-

lar distention on cardiac energetics and coronary flow can also be gauged (in the dog) by inserting into the left ventricle a balloon inflated to different degrees of fullness (328). The blood may be oxygenated by passing it through a mechanical oxygenator system, an autogenous lung, or through a donor, human or animal. It is believed that isolated hearts generally are in varying degrees of failure (performance characteristics less than those of a normal heart within the chest) and that this can be prevented by a continued interchange of its blood with that of a supporting dog or human. The latter arrangement has been used by Sarnoff (335) and by Garcia-Ramos, Rosenblueth, and their associates (126, 313). A possible explanation for this phenomenon is the loss of myocardial catecholamines in the isolated heart preparation and its replenishment by the cross-perfusion technique (201). In any case, in these varying types of isolated hearts doing work, the coronary vascular bed is largely dilated, for the coronary flow is greatly increased and the coronary A-V oxygen difference greatly decreased over the values for hearts working within the chest. Finally, it is of considerable interest that the heart beat and carbohydrate metabolism of the isolated dog heart can be maintained for prolonged periods by perfusion of the coronary circulation, not with blood, but with gaseous oxygen (55).

Wiggers (796) was one of the first to study the hemodynamics of the coronary circulation and energetics of the heart beating and working in situ in the anesthetized open-chest dog, in which the coronary vessels were naturally perfused from the aorta. By right heart bypass, the extracoronary sinus venous drainage can be quantitated. In this, systemic venous return bypasses the right atrium and ventricle into a reservoir from which it is pumped into the peripheral portion of the pulmonary artery. The coronary venous drainage can be collected by a tube in the right atrium or in the central portion of the divided pulmonary artery (309).

While in some of these preparations the coronary circulation is naturally perfused from the aorta at its prevailing pressure, for many investigations it is desirable to have coronary artery perfusion at constant controlled flow rates or at constant perfusion pressures, or both, the pressures being different from the prevailing aortic pressure. Various expedients have been devised to achieve these ends. The simplest arrangement is to connect the peripheral end of a coronary artery or a branch to a blood reservoir at an appropriate elevation so that it drains into the artery by gravity (249). In another arrangement, air expansion

chambers are used to permit constant pressure perfusion (153). Similarly, one end of a pump may be connected to a local arterial source and the other end of the pump to the coronary artery. Either the perfusion pressure or flow rate can be varied separately. For more complicated systems, pump or pump oxygenator systems such as already indicated for right heart and total heart bypass are used, in which the coronary perfusion pressure is constant. These approaches have the important advantage that they enable the investigator to study separately the peripheral and myocardial factors that regulate flow. As a further separation of those peripheral parameters which determine flow and metabolism in the myocardium, the coronary arteries of the isolated heart, heart-lung preparation, and of the open-chest dog, may be perfused at constant pressure or flow rate, first while the heart is beating, and then while it is in prolonged diastole as the result of stoppage from prolonged cervical vagal stimulation or intracoronary injection of acetylcholine, potassium chloride or citrate (17, 249, 311, 323).

Finally, with the advent of methodologies not requiring use of anticoagulants or the insertion into a vessel of a flow metering device, reasonably satisfactory measurements have been made in the resting and active dog (159, 212) and the resting human (92, 319).

Coronary Flow Methods (Animals)

PHASIC FLOW. These were designed with the hope of analyzing the factors affecting coronary flow which are too rapid in action to be studied effectively by mean flow measurements. They record the instantaneous flow at the point of their insertion into a blood vessel. The vascular bed of the heart is made up not only of vessels within the myocardial wall, but also of vessels lying on the surface of the heart. Since the change in mean vessel bore during a cardiac cycle in the superficial vessels (in which the flow measurement is made) is presumably different from that of the deeper vessels, such a device measures a combination of "intramural" and "extramural" flow. It does not, therefore, necessarily indicate correctly the intramural flow at all times. Comparison, however, of the arterial blood pressure with the flow in late diastole in such recordings is the only means known to the author by which change in the active vasomotor state of the coronary bed can be estimated when the coronary arteries are naturally perfused from the aorta.

Some of the major earlier phasic flow methods

which were used on isolated hearts or anesthetized animals have been: *a*) estimation of the phasic difference between the central and peripheral coronary pressure curves during a cardiac cycle (151, 153); *b*) the recording of movement of the free end of a bristle mounted in the wall of a tube of fixed diameter through which coronary flow occurs (302); *c*) measurement of cooling by air of a heated platinum wire mounted in the neck of a bottle partially filled with blood, the lower part of which is connected to the coronary circulation (10); *d*) measurement of cyclic movement of various foreign substances (toluene, mercury droplet) inserted into a coronary artery (10); *e*) recording of the small pressure drop in a pressurized air-blood chamber as blood flows from the base of the reservoir into a coronary artery (93, 153); *f*) measurement of the lateral pressure difference above and below an area of constriction (orifice) in a metal tube inserted into a coronary artery (153); *g*) recording of the upstream and downstream pressure difference in a metal tube inserted into the coronary sinus (196).

Finally, the electromagnetic flowmeter has been successfully applied to the coronary circulation in the dog (217, 395). A square-wave type of electromagnetic flowmeter has been found quite useful in coronary flow studies in open-chest sacrifice dogs (81), but because of their necessary size, they have not yet been chronically implanted on the coronary arteries. The sine-wave type can be miniaturized, and flow transducers of aspirin-tablet size or smaller have been successfully applied for periods of weeks to the right coronary artery, the main left coronary artery and its major branches, of the conscious and active dog (212). For further discussion of flowmeters see Chapter 38 in this *Handbook*.

MEAN FLOW. The most accurate measurement of mean coronary venous outflow is by its collection in a graduate, and of coronary arterial inflow by reading the graduations on a calibrated reservoir. More sophisticated devices have been developed and applied to dog and man. Some of the more important in the dog are: *a*) timing visually or photoelectrically the passage of an air bubble through a glass tube of known length and volume which is placed between the cut ends of a coronary artery through which flow is being measured [bubble flowmeter (90)]; *b*) recording the position of a "float" in a vertical tapered tube through which coronary blood is flowing [rotameter (153, 345)]; *c*) recording the temperature difference of two thermojunctions mounted in a plastic sleeve of constant cross section through which coronary blood is

flowing (thermostromuhr—though its ultimate reliability in many circumstances has been questioned) (153); *d*) recording the heat clearance or the temperature difference of a reference cold thermocouple and an electrically heated thermocouple inserted into the myocardium (143).

Coronary Flow (Man and Animals)

Variations of the Fick principle and coronary cine-angiography have been used to attack the coronary blood flow problem in man. The first major advance came with the use of nitrous oxide inhalation for determining blood flow draining into the coronary sinus. As compared to direct measurement of coronary blood flow, the method [see previously cited reviews: (35, 92, 154, 319)] shows a reasonable accuracy, and in humans has furnished almost all our information regarding coronary blood flow. Another variation of the Fick principle has been used to estimate myocardial blood flow in the animal and in man. Studies in the rat and dog have indicated that when intravenous slug injections of the radioisotopes K^{42} or Rb^{86} are made, the following occurs: the isotopes have a large volume of distribution within the myocardium, and, for at least 1 min after a single intravenous injection of the isotope, their coronary venous drainage is negligible compared with their initial deposition; the extraction ratios of the heart and whole body for the isotope are identical. By determining cardiac output by means of this isotope injection, and at the same time determining the fraction of the injected isotope taken up by the myocardium (animal sacrifice and direct counting) within this minute, it is possible to estimate total myocardial blood flow in the dog and rat (185, 234, 330). By comparing the isotope concentrations in different myocardial areas, the regional flow distribution can also be estimated. These results could have a reasonable accuracy. The obstacles, however, to the use of such a method in man without coronary sinus catheterization are formidable. While the isotope is being infused intravenously at a rate designed to keep a constant arterial concentration, it might be possible to estimate, by radiation detection over the precordium and by direct counts on the blood, the increments in myocardial Rb^{86} content and its concentration in the coronary sinus blood. However, the isotope extraction at different coronary blood flow rates is not constant (reported extractions vary from 40 to 70%) and may vary with duration of the perfusion. As yet, these difficulties have not been resolved (245, 274).

The indicator dilution technique for coronary blood flow in man is based on the fact that, when cardiac output is being estimated by means of a device placed over the precordium to pick up the specific activity of a tracer substance such as I^{131} following rapid intravenous injection, the curve produced during the first circulation of the radioactivity, in addition to having two well-defined peaks representing passage of radioactivity through the right and left sides of the heart, respectively, may also have a third small peak closely following that attributed to left ventricular activity. This appears at a time which could represent myocardial blood flow (343, 381). Unfortunately, because of an insufficient time lag, it is difficult to differentiate the peak of precordial radioactivity related to myocardial flow from other rapid changes in precordial activity, such as that resulting from the preceding passage of blood through the left side of the heart, or that due to subsequent recirculation from the most rapid noncoronary circuits (252). Until the true coronary precordial peak in radioactivity can be more sharply defined, it is difficult to place reliance on data obtained with this method as representing coronary flow. A variation of the application of the isotope dilution technique to the problem arises from the observation in both humans and dogs that concentration curves of radioactivity recorded over the heart, following rapid intravenous injection of small boluses of I^{131} , have slower disappearance rates than those obtained by sampling directly from a peripheral artery, such as the femoral (260), the difference being due presumably to the coronary flow.

Finally, special techniques have been developed for selective catheterization of individual coronary arterial branches in intact closed-chest dogs and unanesthetized human subjects by means of special catheters which permit intracoronary injection of radiopaque materials and roentgenological visualization of the coronary vessels (352, 393). Coronary cine-angiography is, at the present time, in a somewhat embryonic stage of development as a research or diagnostic method. Perfusion with the media in appropriate volume and concentration apparently does not result in development of anginal pain, ECG evidence of myocardial ischemia, or photographic evidence of coronary vasoconstriction. However, fundamental hazards in the application of this technique lie in the possibility of inadvertent mechanical occlusion of a coronary artery with the catheter tip and the known moderate vasodilator and cardiotoxic properties of the contrast media. From an investigative point of view, coronary arteriography, even when recorded

continuously by motion picture photography of the fluorescent screen, does not provide a measure of coronary flow and vascular resistance. Such data can, however, provide evidence of change in size and number of visible arterial vessels after administration of various physiological and pharmacological agents. In the presence of a constant blood pressure, such changes would indicate local changes in the vasomotor states although it cannot be currently determined whether these alterations are active or passive. In addition, it is used to study the existence of and change in intercoronary arterial collateral channels in life, since the origin and distribution of collateral channels as small as $100\ \mu$ can be well demonstrated. From a diagnostic point of view, selective opacification of individual coronary arteries provides information on the length and exact location of partial and complete occlusive lesions in major vessels as small as 1 mm in diameter.

DISTRIBUTION OF MYOCARDIAL BLOOD FLOW

Arterial Circuit

As blood is ejected from the left ventricle, it simultaneously enters both coronary ostia and flows via the epicardial coronary arteries to their respective myocardial beds. By direct measurement in open-chest dogs, the left coronary and right coronary arterial inflow approach 85 and 15 per cent, respectively (153). The same relationship also exists in the dog heart-lung preparation and perfused, fibrillating heart, lending physiologic support to the anatomically designated left coronary artery dominance in dogs. While the direct measurement of coronary arterial distribution in man is unknown, coronary arteriography in unanesthetized patients has demonstrated variations in volume of the various coronary arterial beds which correspond quite well with postmortem anatomic studies (84).

Utilizing the bubble flowmeter (90) in both open- and closed-chest acute experiments in dogs, an average left coronary inflow of 65 ml per 100 g left ventricular tissue per minute was found with no significant difference between the two groups. The left circumflex was found to supply an average of 40 per cent, and the anterior descendens about 26 per cent by weight of the left ventricle. Similar values have been obtained with rotameters and in the intact unanesthetized dog with electromagnetic flowmeters. Figures for the contribution of the anterior septal artery flow in the dog can

be estimated by observing the decrease in total left coronary inflow after occlusion of the septal artery or by direct cannulation (265 and Gregg, unpublished observations). In either method, the volume of flow is from 11 to 21 per cent of total left coronary flow.

Radioactive cations (Na^{22} , K^{42} , Mg^{28} , Rb^{86} , Fe^{56}) and anions (P^{32} , I^{131}) and D_2O have been applied to the coronary circulation as a means of determining distribution of blood and plasma flow, and metabolism of the involved myocardial bed. Tissue uptake and turnover rates of the radioactive substances have revealed a heterogeneous myocardial distribution (21, 122, 197, 234, 244, 245). All left ventricular areas including base, apex, septum, and free walls have a 50 to 100 per cent higher uptake and turnover rate than the right ventricle and atria. In descending order of activity are the right ventricle, left atrium, right atrium, His bundle and, lastly, the sino-atrial and atrioventricular nodes. In most instances, the myocardial uptake is nearly instantaneous since a plateau is reached after a single systemic circulation and, thereafter, remains relatively constant with only minor differences between the 20-sec and 10-min determinations. D_2O similarly reaches equilibrium between plasma and tissue water after a single circulation and can also be calculated within 10 to 20 sec following injection (197).

Radio-rubidium (Rb^{86}) has been found to be the most versatile for myocardial flow determinations because of its long half-life ($T^{1/2} = 19.5$ days), rapid myocardial uptake (in exchange for intracellular potassium), and relatively fixed myocardial extraction despite varying arterial concentrations (230, 245). In addition to the tissue concentrations, Rb^{86} and Na^{22} and D_2O have been used for coronary blood flow determinations, and in those instances where checks against a standard reference method (i.e., N_2O and flowmeters) were done, good correlations were obtained (274). Flow values vary from 0.4 to 1.6 ml per g per min, with an average of 0.7 to 1.0 ml per g per min for dog and man, while in rats values four times this have been found, supposedly related to the four-fold greater energy output of the rodent myocardium, i.e., 1.00 joules per g per min versus 0.27 joules per g per min (185).

The Venous Circuit

In addition to the regional differences in rate of uptake, there also exists a concentration gradient between the endocardial and epicardial surfaces, the former having the higher uptake and turnover of

radioactive cations (244). The disparity is most marked in the right ventricle since the concentration of Thebesian vessels is highest in this chamber, and also, a favorable pressure gradient exists for blood to flow from the myocardium to the cavities during systole. It has therefore been argued that this is supportive evidence for utilization of the deep vascular communications of the heart. The role played by the deep vascular structures, however, is probably quite small for several reasons. Balance studies in which an attempt was made to measure coronary inflow and outflow simultaneously with rotameters in the superficial coronary vessels of the open-chest dog have shown that *a*) coronary sinus flow ceases when both the right and left coronary arteries are occluded with the heart beating in situ; *b*) the left coronary artery accounts for all but 5 to 10 per cent of coronary sinus outflow; *c*) 80 to 85 per cent of left coronary inflow is reflected in the coronary sinus outflow while some of the remainder is accounted for by the anterior cardiac veins; *d*) 90 per cent or more of the right coronary inflow drains via the anterior cardiac veins; and *e*) there is no evidence of significant Thebesian drainage of the right coronary system (153). These studies in the open-chest dog are technically quite difficult and although recovery is usually of the order of 80 to 85 per cent (300), comparison of total coronary inflow with outflow in the superficial veins is subject to considerable error. At the same time, in other experiments following acute coronary sinus ligation it was observed that although the lateral wall of the left ventricle was markedly congested, portions of the interventricular septum showed less evidence of congestion. This observation of 20 years ago was not followed up until recently when it was found that the portion of left coronary inflow (about 15%) not recovered in the coronary sinus could be largely accounted for by the fact that a portion of the left anterior atrial artery flow drains into the left atrium, and that most of the septal artery and some branches of the left descendens artery which perfuse the septum drain into the right ventricular cavity (265, 266). The finding concerning drainage of the left atrial coronary flow is in line with observations with an illuminated cardioscope in humans and dogs at the time of cardiac surgery, that very small streams of dark blood can be seen entering the left atrium but not the left ventricle (53).

The deep drainage channels could have an important functional role if they served as arterial channels from the left ventricular cavity to the myocardium during coronary artery constriction or

occlusion, or as venous channels for the whole myocardium in the presence of extensive superficial vein constriction or occlusion. Regarding the first situation, although essentially complete occlusion of the coronary arteries in human beings has been found at autopsy (227), the presence or extent of development of extracardiac arterial collaterals is not known. In addition, with temporary functional separation of one or both coronary arteries from the aorta, no blood flow from the ventricles into the superficial coronary venous system can be demonstrated and the hearts do not survive (153). When dye is injected into the right ventricle in acute experiments, extensive capillary injection on the surface of both ventricles occurs if right ventricular pressure is artificially made to exceed left ventricular pressure (153). Although this could have occurred through the Thebesian channels of the interventricular septum (265), the anterior cardiac veins were not excluded as a portal of entry for the dye. Regarding the second situation, with acute closure of all grossly visible anterior cardiac veins or of the coronary sinus, or both, a considerable reduction in right and left coronary inflow occurs (153). Although the heart, following acute closure of both the coronary sinus and anterior cardiac veins, becomes exceedingly hemorrhagic and progressively weaker, such hearts may survive up to 2 hours. Dogs in which both superficial venous systems have been chronically occluded in a two-stage operation have survived for periods of months. However, that significant drainage occurs through such a route could not be verified, since, at postmortem examination, these hearts exhibited numerous superficial cardiac veins of considerable size which were not previously apparent, and several large extracardiac venous anastomoses, the aggregate cross section of which was estimated to be adequate for venous drainage of the entire heart (153). Until the intracardiac and extracardiac arterial and venous collaterals which appear with coronary arterial or venous ligation have been excluded as flow channels, any conclusion regarding the utilization of deep coronary venous drainage channels in diseased hearts is difficult to reach.

Possible Use of Left Coronary Artery Flow Together with the Chemical Composition of Coronary Sinus Blood as an Index of Left Ventricular Metabolism

It is not possible to quantitate accurately the metabolism of the right ventricle in dog (or man) because its superficial anterior cardiac veins have many exits into the right atrium and their contained

blood is grossly contaminated by blood from the left coronary artery. However, a large drainage of the left myocardium occurs into the coronary sinus and the latter is accessible. Hence, the question of whether the chemical composition of coronary sinus blood together with left coronary inflow can be used as an index of quantitative changes in metabolism of the left ventricle is a very practical and important consideration because of the widespread use by the basic experimenter and the clinical investigator of these measurements for this purpose. To justify such usage, experimental evidence must show, first, that most of left coronary inflow drains into the coronary sinus and that the latter is not significantly contaminated by drainage from the right coronary artery and, second, that its chemical composition approximates that portion of the blood coming from the left coronary artery which does not flow through the coronary sinus.

In the open-chest dog in which no great effort is made to avoid obstruction at the ostium, the percentage recovery in the coronary sinus of left coronary inflow varies from 64 to 83 per cent in any one dog, and shows little variation from dog to dog (153). By use of a special cannula which collects all the blood draining into the coronary sinus without obstruction to any of its veins, the percentage of left coronary artery inflow recovered in the coronary sinus is quite high (80–90%) and reasonably constant during the induction of a variety of physiological variables and drug injections (300). In the open-chest dog, the right coronary artery contributes not more than 2 to 3 per cent, or 1 to 2 ml per min, to the coronary sinus flow, and this only occasionally. This has been determined by observing minimal changes in coronary sinus flow when the right coronary artery is clamped in the presence of an elevated right ventricular pressure from pulmonary artery stenosis, when right coronary artery clamping is superimposed on a pre-existing occlusion of the left coronary artery (153), and by observing only minimal changes in the optical density of coronary sinus blood following massive injection of Evans blue dye into the right coronary artery (300).

The investigation of whether the coronary sinus fraction of blood is representative in chemical composition of total left coronary venous return started with the experiments of Evans & Starling in 1913 (106) and has continued to the present time. Actually, investigations during this period did not directly attack the problem (158). In these experiments, the effect of increased right ventricular pressure was determined on flow

and oxygen content of coronary sinus blood and of the remaining coronary venous blood including that from the right coronary artery. Obviously, these observations are germane only to the problem of whether an increase in right ventricular metabolism associated with increased right ventricular pressure is reflected in the coronary sinus blood (195, 264). This might not be expected because of the very small drainage of right coronary flow into the coronary sinus. These experiments are certainly not germane to the problem of whether the two coronary venous drainage fractions from the left coronary artery have the same chemical composition, for such measurements were not made.

This question for the left myocardium has been answered by simultaneously and continuously measuring, under different circumstances, left coronary artery flow, and the flow and oxygen content of the two coronary venous fractions derived from the left coronary artery. In these experiments, the systemic venous return bypassed the right heart, and the right coronary artery was generally clamped. The oxygen uptake calculated on the basis of left coronary artery flow times the difference between the arterial and coronary sinus oxygen content agrees quite well with the oxygen uptake based on the sum of the respective volume flows and the oxygen content of the two left coronary venous drainage fractions. This is effected by a combination of a generally lower oxygen content in the coronary sinus and a considerably greater coronary sinus flow (300). Hence, in the open-chest dog a combination of left coronary artery flow and coronary sinus arteriovenous oxygen difference gives a reasonably precise value for uptake of oxygen by the left ventricle.

From data such as these it has been reasonably assumed that measurement of coronary sinus flow could be substituted for left coronary inflow and, together with the coronary sinus, A-V oxygen difference could also serve as an index of metabolic events in the left myocardium of man and beast. The authors, however, in no way recommend this procedure. Although widely used in man, it has never been demonstrated that the flow, composition, and sources of coronary sinus blood fulfill the requirements as laid down and found to exist in the dog. [Actually in early experiments with the isolated dog heart significant right coronary artery drainage into the coronary sinus was demonstrated (92).] In addition, accurate measurement of coronary sinus flow is extremely hazardous whether done indirectly by means of the nitrous oxide method or directly by

cannulation. In the first case there is the ever present danger of contamination with right atrial blood. In the second instance, without knowledge of the investigator, coronary sinus flow may be reduced by shrinkage and partial closure of the sinus. This diminishes only slightly the left coronary inflow, which now drains preferentially by the anterior cardiac veins.

PHYSICAL DETERMINANTS OF CORONARY FLOW

Coronary flow is related to the pressure difference (effective pressure) between the central coronary artery (identical to aortic pressure) and the right atrium divided by the sum of the viscous resistances to flow in the epicardial portion of the artery and in the peripheral coronary bed. Viscous resistance to flow, aside from change in hematocrit, is mainly governed by the mean caliber of the coronary vascular bed. Since the arterial resistance is negligible, the mean coronary diameter and, hence, flow are controlled by the effective intravessel pressure and by two peripheral mechanisms, i.e., active changes in the state of the small mass of intramural smooth muscle built into the coronary vessels, and the mechanical or passive effect on flow exerted during ventricular systole by the large muscle mass around the coronary vessels.

Insight into the complexity of the integrating action of central and peripheral flow determinants has been obtained from the recording of the peripheral coronary pressure and the phasic or moment-to-moment changes in coronary inflow and outflow in the epicardial arteries and veins (151, 153, 158, 212, 301). These curves were obtained from the open-chest dog and from the resting unanesthetized dog some days postoperatively, after implanting an electromagnetic flowmeter on the left coronary artery (fig. 6). At the onset of isometric contraction of the left ventricle in the unanesthetized dog, there is an abrupt decrease in left coronary inflow and, although at times backflow may appear, a considerable forward flow generally persists throughout systole. With the rise in aortic pressure, forward flow increases initially and rapidly, only to decrease to a new intermediate level in late systole. With the onset of isometric relaxation, coronary flow increases significantly, peaking at early diastole and then declining progressively. These demarcations of flow are much less obvious in the right coronary inflow pattern, which roughly resembles the prevailing aortic pressure curve. The flow

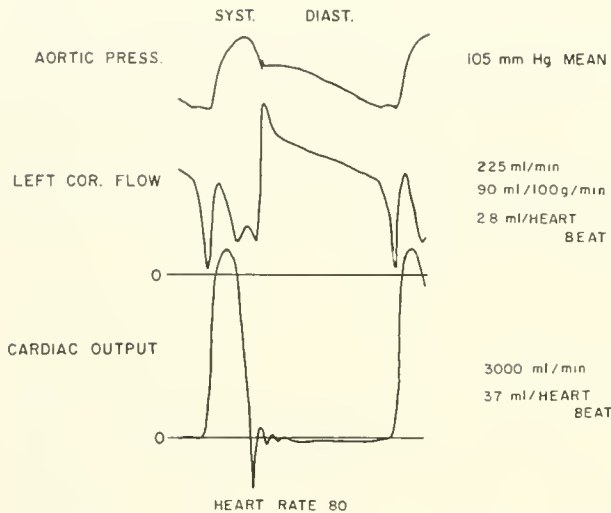


FIG. 6. Reproduction of a retrace of an original record taken in the conscious dog, 14 days postoperative, showing phasic aortic blood pressures recorded by a strain gauge connected to a chronically implanted aortic catheter, and phasic left coronary artery flow and stroke cardiac output by electromagnetic flowmeters chronically implanted, respectively, on the main left coronary artery and ascending aorta. (Unpublished observations.)

patterns just indicated for the conscious dog are similar to those in the open-chest dog except that in the left coronary artery of the latter, systolic flow is minimal and backflow is usually present during isometric contraction (153).

The flow patterns of the left coronary artery are a complex of events happening in the total distribution of flow in the left myocardium and a small portion of the right ventricle. Regional variations of flow pattern might be expected based on anatomical and functional differences in the areas supplied. Flow patterns of the main left coronary and its circumflex and descendens branches are essentially similar. Phasic flow, however, in the left anterior atrial artery shows a forward flow in both systole and diastole with the flow pattern resembling an aortic pressure pulse (349). About 40 per cent of this arterial flow (5% of left circumflex flow) drains into the left atrium (266). Patterns of flow through the canine septal artery are not available. It would, however, be predicted that the pattern would differ from that in the circumflex and descendens by having a much smaller systolic flow since this artery has essentially no epicardial component. Most of the flow in this very small artery drains into the right ventricle (265).

The finding of a significant and variable coronary flow during systole in the left coronary artery of the unanesthetized dog deserves further comment. In the

past, the view based on work in the open-chest dog has been that flow in the left coronary artery is very small during systole, that it does not vary significantly with different dynamic conditions, and that it can be accounted for largely on the basis of radial enlargement of the epicardial vessels and their filling during ventricular contraction (153). This meant that events in systole could be and were largely ignored and that the only important considerations for regulation of left coronary flow were happenings during diastole. Recent work using chronically implanted electromagnetic flowmeters indicates that although the coronary flow in systole in the unanesthetized dog at rest can, at times, be rather small, in many dogs it may approximate 30 per cent of that during diastole. In the presence of mild exercise, it does not appreciably increase, but following release of coronary artery occlusion, and during excitement and chronic stimulation of the cardiac sympathetic nerves, the volume of systolic flow increases 300 to 400 per cent, as does the diastolic flow, the ratio between the two remaining about the same (139, 212, 301). Finally, in irreversible hemorrhagic shock, late in the period of spontaneous cardiovascular decay after blood reinfusion, the systolic flow may approach that during diastole for an equivalent time interval, and eventually the flow pattern may resemble somewhat the prevailing aortic pressure pulse with most of the coronary flow occurring in systole rather than in diastole (159). The proper explanation of these findings awaits future experimentation (fig. 7).

The preceding account indicates that the coronary bed has a fluctuating resistance to flow. Flow curve inspection shows the obvious importance of left ventricular contraction in controlling coronary flow, because during systole left coronary flow is reduced while coronary sinus flow is increased. The increase in coronary sinus flow suggests that ventricular contraction acts to aid coronary flow by massaging blood through its wall; the reduction in coronary inflow suggests that it acts to throttle coronary flow. The answer depends upon the relative changes of inflow and outflow volume during systole. Unfortunately, this is impossible to determine because of the incomplete and variable drainage of the left coronary artery through the coronary sinus. However, actual measurements in the left coronary artery of the open-chest dog show that the peripheral coronary maximal systolic and minimal diastolic pressure values approximate 80/20 mm Hg, and inflow is cut off at these pressure levels when the left coronary artery is perfused through its distal end under constant pressure.

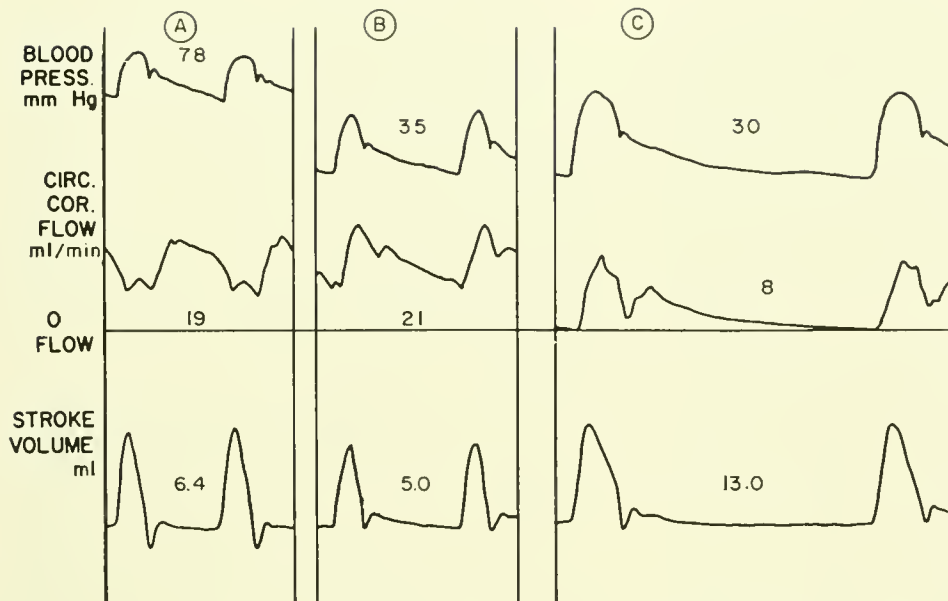


FIG. 7. Reproduction of retraces from an original record taken in a resting unanesthetized dog some days postoperative showing the effect of irreversible hemorrhagic shock on phasic blood pressure and phasic stroke left circumflex coronary flow, using a strain gauge and electromagnetic flowmeter as in fig. 6. *A*—early; *B*—midway; *C*—late in the period of spontaneous hemodynamic decay following reinfusion. (Unpublished observations.)

In the right coronary artery, the contour and time relations of the peripheral coronary pressure curve are similar but the values for systole and diastole and for the cut-off of flow are considerably lower (153).

Separation and quantitation of the determinants of coronary flow lying within the myocardial wall, i.e., the vascular and extravascular muscle, are of extreme importance. Various methods have been proposed and used, but they have been only partially successful. The problem of determining the relationship of blood flow to active vasomotor changes, irrespective of whether the effect on the intrinsic muscles of the coronary vessels is mediated through the blood stream or is secondary to metabolic changes in the surrounding myocardium, is especially difficult. It is not known how much coronary flow might change with a given change in coronary perfusing pressure without an associated active change in the vasomotor state of the bed. Determination of active variations in vasomotor tone in the coronary bed is further complicated by uncontrollable mechanical factors. Variations may occur in the respective durations of systole and diastole during which the rates of flow per unit of time may be quite different and thus obscure any active vasomotor changes.

By analysis of phasic inflow curves, however, change in the vasomotor state can be separately and

roughly estimated. A critical point on a coronary inflow curve is selected in late diastole, at which time the rate of change of the volume-elastic and myocardial compression forces is presumed to be minimal (153). At this point, extravascular forces are at a minimum, the rate of flow reflecting the vasomotor state of the coronary bed, and the ratio of the aortic pressure to the simultaneously existing rate of flow is then determined. A shift in the diastolic ratio is taken to represent active constriction or dilatation of the coronary bed (41, 146). It has also been suggested that change in the extravascular compressing force during systole can be estimated by comparing the diastolic ratio with the ratio of blood pressure to coronary flow at a point in late systole when extravascular support is maximal and flow reflects the combined effect of myocardial compression and the existing vasomotor state (146). At this time, the rate of change of the volume-elastic and myocardial compression forces is presumed to be minimal. Use of such a systolic point has as yet no experimental verification.

The problem of determining the magnitude of extravascular support has been approached in different ways. It has been suggested that intramural pressure can be used as a measure of extravascular compression, and attempts have been made to quanti-

tate the pressure developed within the wall of the left ventricle during systole and to use it as a measure of extravascular support. To do this, pressure pulses have been recorded from a myocardially imbedded vessel (or myocardial fluid pocket connected to a recording manometer). However, experimental work indicates that although these pressures may indicate directional changes in extravascular compression, they are, in part, artifactually produced and, hence, do not approximate the correct values for intramural pressure (153).

A method recently developed has given some information on this point (323). Continuous measurements are made in the open-chest dog while the left coronary artery is perfused with blood under a constant pressure. First it is done in the beating heart, and then during ventricular asystole induced by vagal stimulation, or by disconnecting an external pacemaker which drives the ventricles (complete atrioventricular heart block having been surgically produced previously). By either means, the mechanical effects of ventricular contraction are largely removed. Induction of ventricular asystole by vagal stimulation always increases immediately (within 1 sec) left and right coronary inflow. Thus, ventricular contraction acts to impede coronary flow through the ventricular wall. The extent of the rise of flow is taken to represent the magnitude of the mechanical or passive factors limiting coronary flow. The magnitude of this mechanical throttling effect on coronary flow during systole normally varies from 31 to 300 per cent and averages about 50 per cent. The new flow level represents that state of coronary dilatation related to the condition of the intrinsic smooth muscle of the coronary vessels at the prevailing coronary pressure. The relative contribution of extravascular and intravascular resistance to an increase of coronary flow has been tested under the different conditions of increasing heart rate, decreased arterial blood oxygen saturation, aortic constriction, transfusion, and drug injections. In all instances, the major portion of a flow increase is through active dilatation and not through reduction in extravascular resistance. The largest reduction (40%) in extravascular resistance is from a decrease in arterial oxygen saturation (155, 236).

DETERMINANTS OF NORMAL MYOCARDIAL METABOLISM

The ability of the heart to do work depends basically on its biochemical activity leading to muscular

contraction. Cardiac muscle has been found to have basic chemical patterns similar to those of other muscle. The catabolism of fat, carbohydrate, and protein produces free energy, about half of which is dissipated as heat and half is captured as phosphate-bond energy which is used for muscle cell work and for various anabolic activities such as synthesis of glycogen, lipids, proteins, and enzymes. These catabolic and anabolic reactions proceed simultaneously under the influence of a complex system of enzymes, coenzymes (from the vitamin B complex), and hormones.

Coronary sinus catheterization studies in man and dog have indicated that the heart is able to choose its fuel from a variety of foodstuffs. These include mainly glucose, lactate, pyruvate, fatty acids (non-esterified) and, to a lesser extent, acetate, ketone bodies, and amino acids. To determine their quantitative contribution to the energy production of the heart, i.e., its oxygen consumption, measurements have been made of their cardiac extraction (coronary artery—coronary sinus difference), their total uptake [coronary flow \times (coronary artery—coronary sinus difference of substance)], and the myocardial respiratory quotient (coronary sinus—arterial carbon dioxide difference; coronary artery—coronary sinus oxygen difference). Excellent correlation has been demonstrated between the myocardial respiratory quotient and the myocardial uptake of substance. The extent to which each substrate contributes to the energy requirement of the heart in vivo is influenced by its concentration (above threshold) in arterial blood. In addition, the state of nutrition of the organism markedly influences the kind of substrate used for energy production of the heart. Under postprandial conditions, or after glucose infusion, myocardial metabolism is mainly glucose, lactate, and pyruvate, since its respiratory quotient approximates 0.9 with a high extraction of carbohydrate and a negligible uptake of amino acids. Even the substitution of 5 to 10 per cent oxygen for the normal 21 per cent in the inspired air does little to change carbohydrate uptake by the normal heart. During overnight fasting, the heart derives much of its energy from fat, as indicated by a myocardial respiratory quotient of 0.80 with a low extraction and uptake of carbohydrate. With prolonged fasting, the extraction coefficient for carbohydrate practically disappears, those for fatty acids and ketones are maximal and the respiratory quotient is 0.70. As regards the uptake of oxygen, the coronary A-V oxygen differences in man vary linearly with the arterial oxygen content through a range from mild

anemia to marked polycythemia so that the myocardial extraction coefficient ($A-V$), A is constant.

In addition to patterns of myocardial metabolism in the normal heart, other metabolic changes have been reported in some pathological and diseased states. Patients with heart failure and decreased cardiac work due to valvular disease show an increased carbohydrate uptake by the heart with a normal extraction of lactate and pyruvate and increased glucose extraction. The heart in the patient with diabetes appears to derive most of its energy from fat even in mild cases with a postabsorptive respiratory quotient of about 0.7 and an increased uptake of fatty acids and a decreased carbohydrate uptake.

Thus, the heart demonstrates broad flexibility in the utilization of substrate for energy production without a change in work performance or work capacity. This makes it largely independent of fluctuations in its chemical environment. There is no evidence that substrate lack occurs in any clinical situation to the extent that it embarrasses the cardiac work capacity. Similarly, the metabolic disturbances such as diabetes mellitus which alter the fuel mixture available to the heart do not also alter cardiac function. It is, however, well to defer detailed consideration of other data because an interpretation must be based on the assumption that oxidation of foodstuffs to carbon dioxide and water is the sole factor in the determination of the myocardial respiratory quotient and of the myocardial extraction and uptake of these compounds including oxygen. Without doubt, storage of and/or conversion into other compounds is occurring concurrently, and these activities are especially prominent in the presence of a changing cardiac level of activity or changing levels of blood substrate (16, 32, 33, 74, 116, 133, 169, 278, 279).

BASAL DATA

In the resting state, the coronary data for dog and man agree. With the left ventricular cardiac work index approximating 3.0 to 4.6 kg-m, left coronary flow approximates 72 to 85 ml per 100 g of left ventricle per min (118, 153, 307). In the anesthetized open-chest dog, values as high as 600 ml per 100 g left ventricle per min have been recorded when the left heart has been stressed by a combination of catecholamine injection and aortic constriction (344). Left coronary flow values in the unanesthetized dog during maximal natural stresses are not yet available but during moderate treadmill exercise and following

excitement, the coronary flow has approximated that in the open-chest dog (212). As indicated under physical determinants of coronary flow, the fractionation of the volume flow between systole and diastole is somewhat variable, but in the left coronary artery of the unanesthetized dog the systolic volume flow very often approximates 25 to 30 per cent of the diastolic flow under semibasal conditions, as well as during excitement, exercise, and reactive hyperemia (159a).

In the anesthetized dog, the circulation time from the central coronary artery to the coronary sinus approximates 4.5 sec (260). In normal patients, the coronary transit time (with I^{131} injection) varies from 6.5 to 11 sec. Exercise and nitroglycerin, which increase coronary flow (nitrous oxide method), decrease the transit time (increased coronary flow velocity) while the Valsalva maneuver, which increases the circulation time, decreases coronary flow (135).

Flow values for the right coronary artery in a good-sized open-chest dog approximate 10 to 15 ml per min. In the resting, unanesthetized dog, the values are similar (unpublished observations). The volume of systolic flow generally exceeds the diastolic volume flow for an equivalent time period and very often exceeds total diastolic flow (153, and unpublished observations). Values per gram of myocardium and the flow responses to natural stresses of everyday life are not known.

Although each ventricle can remove essentially all oxygen from the coronary blood in its passage through the myocardium, normally, for the left ventricle (also the right), about two-thirds is extracted with an arteriovenous difference of 11 to 14 ml, and a coronary sinus value of 5 to 6 ml. This extraction changes little, i.e., less than 10 to 20 per cent with increased stress (except following catecholamine injection, anoxia, and anemia, in which it decreases), indicating that the oxygen supply is well balanced with metabolic demands (208).

Oxygen uptake per 100 g left ventricle (coronary flow \times coronary $A-V$ O_2 difference) is 8 to 10 ml per min in the open-chest dog, the anesthetized closed-chest dog with normal blood pressure and cardiac output, and in the resting unanesthetized dog and human. Maximum values calculated in the open-chest dog approximate 60 ml per 100 g per min. In the unanesthetized active dog under the influence of mild exercise and excitement, values are not available.

With present poor methodology, separation of oxygen usage between systole and diastole can only be

made by measuring oxygen uptake, first in the beating heart during repetitive systoles and diastoles, and then in the relaxed heart or during prolonged diastole, thus obtaining the oxygen usage during systole by difference. Estimation of the metabolism of the myocardium in the absence of a heart beat, that is during prolonged diastole, has been made in the vagus-arrested heart (see section on Physical Determinants of Coronary Flow). The oxygen saturation of the arterial blood and coronary sinus blood is also measured continuously. This permits left coronary arteriovenous oxygen difference as well as coronary inflow to be measured continuously, first in the beating heart and then in the stopped heart until a new equilibrium is established, usually within 20 to 25 sec (155, 156, 249). As coronary inflow rises immediately with asystole, the oxygen saturation of blood in the coronary sinus also rises, thus greatly reducing the coronary arteriovenous oxygen difference. Calculations in many experiments show that as the result of the combination of an increased coronary flow and a decreased coronary arteriovenous oxygen difference, the oxygen usage per 100 g of left ventricle per min decreases from the average control level of 8.1 ml in the working beating heart to 2.3 ml in the resting heart, or to 30 per cent of the control. This oxygen consumption in diastole is about one-third that in systole for an equivalent time period (249).

Attention is also directed to the values for oxygen usage obtained in the same type of preparation but in which the external work of the heart is reduced to zero by other means. In the potassium-stopped heart, the oxygen usage of 2 ml during diastole is about the same as in vagal asystole. In the beating heart emptied by suction and hemorrhage, and in the heart with induced ventricular fibrillation, the oxygen usages of 3.4 and 3.8 ml are much greater (249) (see the paragraphs under Heart Rate for more detailed consideration).

The metabolism of the heart is predominantly aerobic. With abrupt vagal stoppage, however, during constant pressure perfusion of the coronary arteries, an excess of oxygen (oxygen debt) over that in the asystolic state is taken up by the heart from the onset of asystole to the time of appearance of the final resting metabolism. This volume of oxygen, which is quite small (estimated as 8% compared to the maximum oxygen debt for an equivalent weight of skeletal muscle of man), might be greater in a heart working to capacity. Whether under prolonged hypoxia the anaerobic component of myocardial metab-

olism can be extended has not been determined (155).

As in any muscle, the mechanical efficiency of the left ventricle is estimated by dividing its external work by the difference between its oxygen consumption during activity and during its resting state. Published data (31) which indicate efficiency approximating 10 to 20 per cent in the normal heart include only the first two measurements. Since the resting metabolism is considerable and variable, and such values are generally not available, interpretation of the relation of cardiac work to oxygen uptake is difficult.

RESPONSE OF THE CORONARY CIRCULATION TO VARIOUS STIMULI

The information has been obtained from the unanesthetized dog and man and from the anesthetized open- or closed-chest dog.

Resting State

As already pointed out, the levels of coronary flow and oxygen usage of the myocardium are quite fluctuant, varying greatly with the different types of preparation and the prevailing stimuli. For values of coronary flow and myocardial metabolism representative of the basal or resting state, selection of data in the dog and man must be restricted to those in which the systemic arterial blood pressure, cardiac index, cardiac work index, heart rate, and body oxygen uptake roughly approximated those figures for the resting state. In the abnormal or diseased state in human beings, data have been restricted to those in which systemic blood pressure, cardiac index, cardiac work index, and heart rate approximate values regarded as acceptable for the basal state when there was no known reason for it to be elevated. These criteria exclude a considerable volume of published work, especially in man. While most of the data comparing left coronary flow to the oxygen usage per 100 g left ventricle per min, for the resting state in man and dog, have been obtained by the N_2O method, the excellent correlation of A-V oxygen differences yielded by this method with those from the more precise methods used on the dog supports the accuracy of the former when properly used.

Reactive Hyperemia

Reactive hyperemia is considered to be the excess blood flow (over the control flow that normally would have occurred) following release of a coronary artery occlusion. The coronary bed is extremely reactive to the stimulus of anoxia. After release of temporary occlusion of a coronary artery, even for as short a time as 2 to 3 sec, left coronary arterial flow increases almost immediately in the isolated heart, heart-lung preparation, the anesthetized open-chest dog, and the unanesthetized dog (66, 67, 147, 301). The augmented flow exists throughout systole and diastole. The flow response occurs without necessarily any change in blood pressure or heart rate and before any impairment of myocardial contraction occurs in the area rendered ischemic. Beyond 30 to 60 sec of occlusion, the area bulges during systole (153). Depending upon the duration of the occlusion, the peak flow response (100–300 % of control flow) does not usually

occur immediately upon release of the occluded coronary artery, but reaches a maximum some time during the first half minute of reactive hyperemia and may last up to 4 min (fig. 8). The volume of reactive hyperemia blood flow, its duration and peak flow values increase with lengthening periods of left circumflex arterial occlusion up to 120 sec. The theoretical blood flow "debt" (control blood flow \times duration of occlusion) seems to be always greatly overpaid (average 219 %) in the presence of periods of occlusion lasting from 5 sec to 180 sec. The reactive hyperemia responses in skeletal muscle vascular beds are similar (222) except that the blood flow debt is variably over- or underpaid (410). In other vascular beds, such as the superior mesenteric artery, this response is much smaller than in the myocardium; in the renal (150), it is essentially nonexistent.

The presence of reactive hyperemia has not been satisfactorily explained. Its purpose must be to supply

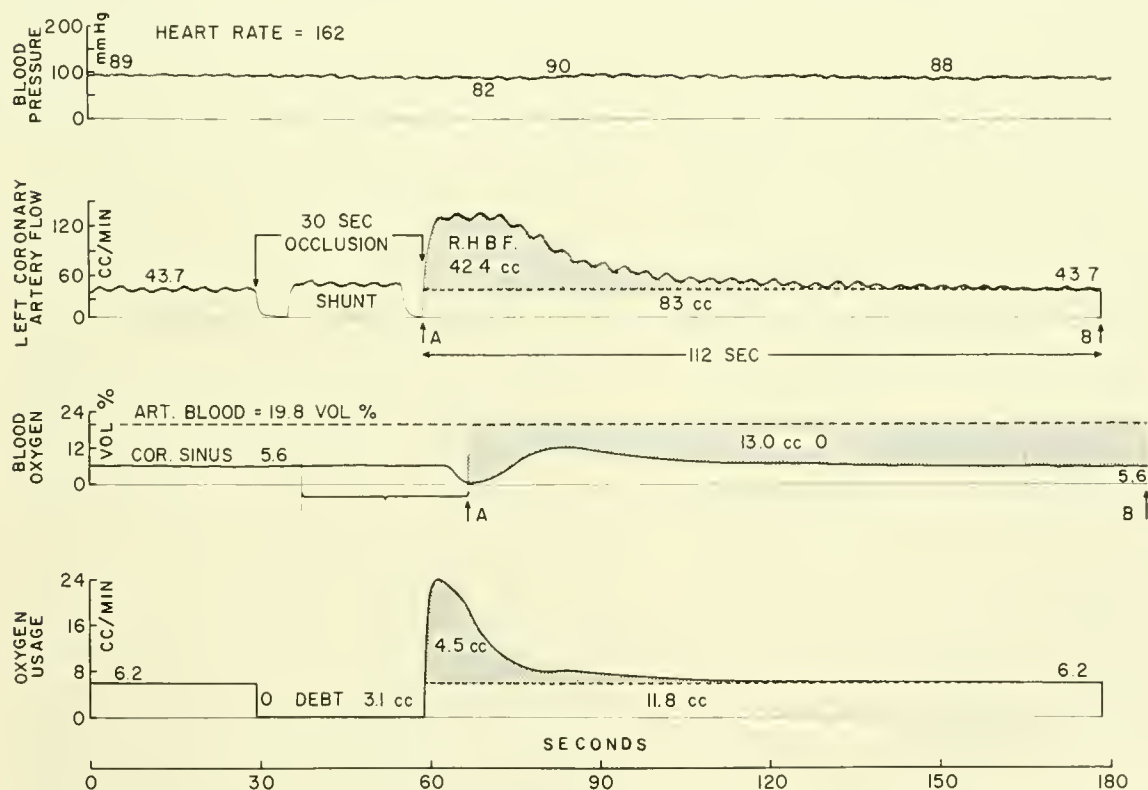


FIG. 8. Diagrammatic redrawing of arterial blood pressure (upper tracing), left coronary blood flow (next lower tracing), and coronary sinus oxygen saturation (third tracing down), before, during, and after release of 30 sec of left coronary artery occlusion in the open-chest dog. Lowest curve represents O_2 consumption of left myocardium (flow times A-V O_2) in ml/min, calculated from above experimental data. Arrows A and B represent, respectively, beginning and end of measurements of reactive hyperemic blood flow (RHBF) and its average A-V O_2 difference used in calculation. [From Coffman & Gregg (67).]

the metabolic needs accumulated during the anoxic period. The large increase in systolic as well as diastolic flow within the first few seconds, before there is time for a change in myocardial contractility, indicates that massive active vasodilation has taken place which overcomes systolic flow resistance. With a longer period of occlusion, there must be considered the possibility of flow through arteriovenous shunts and through vessels probably near the epicardial surface, whose surrounding myocardium is now "tired" and does not so strongly oppose flow.

The oxygen consumption during myocardial reactive hyperemia is measured by determining the left coronary artery blood flow (rotameter) and the difference in oxygen saturation of the arterial and coronary sinus blood (measured continuously with an optical densitometer). The theoretical oxygen "debt" (control oxygen consumption \times duration of left coronary artery occlusion) is overpaid for 15- and 30-sec but slightly underpaid for 10-sec occlusions (67). The rate of oxygen consumption during the increased blood flow period is greater than in the control state, showing that the myocardium has been stimulated to take up more oxygen. The basic hypothesis governing the calculation of the oxygen "debt" in these studies is somewhat erroneous, for the oxygen in the blood in the coronary vascular bed during arterial occlusion, the metabolic rate during the circulatory stasis, and changes in cardiac work are not considered. As further evidence that the myocardium develops an oxygen deficit, i.e., that anaerobic metabolism occurs, it has been found that lactic acid increases in the coronary sinus blood, often in comparison to pyruvic acid levels following the period of anoxia (67). These observations have been confirmed in the unanesthetized dog with the aid of chronically implanted (3-14 days postoperative) electromagnetic flowmeters and coronary sinus sampling tubes (280).

The contracting myocardium can withstand much shorter periods of arterial occlusion and oxygen deficit than resting skeletal muscle, and repays its oxygen "debt" with an increased blood flow but with a decreased A-V oxygen difference.

Heart Rate

Early reports indicated that myocardial oxygen usage increases in the heart-lung and isolated heart when heart rate spontaneously changes or when it is increased by warming the sinus node or by driving the heart electrically, but the evidence was conflicting

concerning the effect of rhythm of the heart on coronary blood flow. In the above preparations, increase in heart rate either increases, decreases, or does not affect coronary flow (10). More recent investigations with somewhat better techniques and methodologies confirmed this finding of correlation of oxygen usage with heart rate in these preparations and showed a higher energy cost of external work at the faster heart rate (369). The oxygen observations were extended to the empty heart beating in the open-chest dog (249). In the latter preparation, electrically induced ventricular tachycardia after section of the bundle of His (23, 236, 355) or electrically induced auricular tachycardia at rates somewhat higher than those naturally occurring generally increases aortic blood pressure, cardiac output, and cardiac work, while the stroke volume and stroke work decrease (225). Simultaneously, minute coronary flow and oxygen usage increase, coronary resistance decreases, oxygen extraction is unchanged, but the coronary flow and oxygen consumption per beat decrease (23). Comparable results were obtained in normal human subjects with atropine-induced cardio-acceleration (137) and in the anesthetized closed-chest dog with electrically induced auricular tachycardia, except that systemic blood pressure, cardiac output, and cardiac work did not rise (256). Since acceleration of the heart means proportionally greater time per beat and per minute in systole than in diastole, and since in systole coronary flow is less than in diastole, it would be anticipated that increased heart rate per se should reduce coronary flow. Since it does not, it must be that increased flow is due to arteriolar dilatation resulting from the increased metabolic activity. Actual measurements indicate that as heart rate increases, extravascular resistance rises but intravascular resistance falls to a greater extent, indicating a fall in net coronary resistance (236). The same trend of flow and oxygen usage per beat and per minute also occurs at the faster heart rate when minute cardiac work is held constant or when comparisons are made at the same level of stroke work. This means that cardiac acceleration can augment the energy metabolism of the myocardium without manifestation of the extra energy as work (23, 225). Data on alteration in the coronary circulation following a naturally occurring change in heart rate are limited to the observation of increased coronary flow with increased heart rate (92). Hence, the value of these observations in relation to natural changes in heart rate arising from local changes in the circulation of

the sinus node naturally occurring remains to be determined.

In the open-chest dog, various arrhythmias, either occurring naturally or induced by electrical means, by mechanical stroking of the heart, or by aconite application, significantly reduce systemic blood pressure and coronary flow when the irregularity is marked or the rate rapid (above 190 per min) (72, 387). These arrhythmias include incomplete heart block, premature auricular and ventricular systoles, auricular fibrillation and flutter, auricular and ventricular tachycardia.

Heart Doing No External Work

Knowledge of the metabolic state of the heart doing no external work is important because: *a*) ventricular fibrillation and asystole are frequent experimental and clinical occurrences; *b*) in the empty beating heart or the asystolic arrested heart, the magnitude of oxygen utilization could seriously affect the potential for normal external efficiency of the myocardium; *c*) with the advent of open-heart surgery one must be certain, in the hearts made dynamically quiescent by means of cardiac bypass, ventricular fibrillation, or ventricular arrest, that the metabolic requirements are met by the available oxygen and myocardial damage does not occur.

The relative length of time the A-V node and myocardium can withstand complete ischemia and still function normally on return of their blood supply has been studied in dogs whose hearts were maintained on an extracorporeal circulation. Myocardial anoxia (by clamping the coronary inflow) leads to somewhat earlier damage to the myocardial muscle than to the conducting system, for after 80 to 90 min of anoxia, blood pressure cannot be maintained on removal of the heart from the extracorporeal circulation, while conduction is normal after as much as 100 min of anoxia. The former is due to development of an unusual firmness of the left ventricular muscle which is not reversible upon reperfusion of the heart (65). At the same time, ventricular distensibility, as revealed by ventricular pressure-volume curves, is sharply reduced (161). If ventricular fibrillation is induced without maintenance of coronary flow, myocardial substances such as adenosine triphosphate and glycogen (which are maintained with coronary perfusion) fall progressively within 15 to 30 min and are partially resynthesized upon reinstitution of perfusion (288). The oxygen usage has been determined for the left ventricle, the external work of

which has been reduced to zero by four different procedures—vagal stimulation, intracoronary potassium injection, ventricular fibrillation, and hemorrhage combined with suction to give an empty but beating heart. Results have been rather variable for the same procedure in the hands of different investigators and generally one investigator has used only two of the procedures. For example, the values for oxygen usage for 100 g myocardium during fibrillation vary from 3.7 to 14.6 ml, in the empty beating heart from 1.5 to 3.5 ml, during vagal asystole from 0.8 ml to 3.7 ml, intracoronary potassium injection from 1.4 to 2.5 ml (17, 22, 26, 29, 179, 192, 249, 268, 288, 369). However, comparing the four procedures in the same series of experiments using the open-chest dog, the oxygen uptake per 100 g left ventricle in the working heart is 8 to 10 ml per min, the resting metabolism (absence of heart beat, cardiac output, and arterial blood pressure) during cardiac arrest by vagal stimulation or potassium injection, approximates 2.5 ml per 100 g left ventricle per min, or about 25 to 30 per cent of that at the prior working level (249). The metabolism of the nonworking (but slowly beating) heart obtained by rapid exsanguination is about 3.4 ml, and of the fibrillating heart 3.8 ml. Where measured, oxygen values were the resultant of a simultaneous coronary flow increase and coronary A-V oxygen decrease. Although the relative values may hold, too much stress should not be placed on the absolute values. While the various determinants of each are probably still largely unknown, knowledge is sufficient to indicate that each should be widely variable. For example, values for the empty beating heart are grossly affected by the prevailing heart rate; values for the fibrillating heart depend upon the type and frequency of fibrillation and upon the ventricular diastolic size (268); values for the vagus-arrested heart or following removal of an artificial pacemaker are not affected by ventricular systolic or diastolic size but vary greatly with the previous level of metabolism in the working heart. With a large elevation of myocardial metabolism by intracoronary artery injection of epinephrine or norepinephrine, the values are especially high and may equal 50 per cent of those in the control state (249).

Ventricular Volume or Fiber Length

Correlation of the left ventricular diastolic or systolic fiber length (volume of a ventricle), or ventricular tension, with the coronary flow and oxygen

usage has been the subject of many serious and excellent investigations, but largely with the use of the isolated heart. The hypothesis that the oxygen used during ventricular systole is largely determined by ventricular diastolic volume but not by ventricular tension has been in vogue for many years. In 1927, Starling & Visscher (354) showed that myocardial oxygen consumption correlated with the changing diastolic ventricular volume to the point of diminished stroke volume from excessive ventricular distention, but that the oxygen consumption of the heart had no relation to its systolic volume. In isolated strips of mammalian myocardium, the oxygen consumption at rest increases significantly as the muscle length is extended, but the tension developed as a result of lengthening has a negligible effect on the oxygen usage (396). Recently, others have shown an excellent correlation of oxygen usage and diastolic volume in the excised beating or fibrillating heart with perfused coronary arteries (269). These observations also apply to the heart beating within the chest. For example, following partial constriction (by means of a snare) of the pulmonary artery or the aorta central to the two coronary ostia, the oxygen usage of both ventricles, and the blood flow in right and left coronary arteries, are increased, even the flow in systole being considerably augmented in the right coronary artery (153). However, in the excised heart or the heart in situ which has been stopped by cervical vagal stimulation or potassium injection, this relation does not hold. Here large changes in the volume of blood within the ventricular cavities can occur without alteration of the oxygen consumption (249, 268). This observation ties in with the fact that in the open-chest dog the working heart's oxygen usage and its coronary flow are not determined by the filling pressure (atrial pressure) or the end-diastolic pressure or volume, for at any given filling pressure the oxygen and coronary flow can vary widely (46, 47). In experiments in which the isolated beating heart with perfused coronary arteries has been made to contract isovolumetrically or isobarically, the myocardial oxygen consumption is best correlated with peak systolic pressure or systolic volume (269).

Blood Pressure

CORONARY VENOUS PRESSURE. The venous pressure in the great cardiac vein of the anesthetized dog, with or without open chest, approximates (10–15)/(0–5) mm Hg (153); the values for the coronary sinus and anterior cardiac veins are considerably lower, while

that in the right atrium into which the coronary blood drains approximates 0 to 8 mm Hg. It would be expected that elevation of systemic venous or right atrial pressure would decrease both right and left coronary inflow. However, the influence of these pressures on coronary flow is difficult to study for the changes induced in them lead to other cardiodynamic alterations. An approach to the problem has been made by studying the effect of constriction or ligation of the coronary venous drainage system on coronary inflow. With the heart beating in situ, mild elevation of pressure in the coronary veins draining the left coronary artery by coronary sinus constriction may decrease only slightly coronary inflow and increase coronary A-V oxygen difference. Acute coronary sinus closure causes congestion of the left ventricle (but not of the right ventricle, atria, or a portion of the interventricular septum), a greatly elevated venous pressure in the coronary sinus and great cardiac vein often approximating or exceeding aortic systolic pressure (153), but the flow reduction in the left coronary artery or its major branches is only moderate, averaging 8 per cent in 10 dogs. However, the venous outflow measured simultaneously in several major anterior cardiac veins increases greatly. Similar responses occur when the major venous drainage channels of the right heart, the anterior cardiac veins, are occluded in acute experiments; right coronary inflow decreases from 0 to 63 per cent, averaging 21 per cent in eight different experiments (153).

In acute experiments, pulmonary artery constriction in the presence of previous ligation of the anterior cardiac veins still causes a significant augmentation of right coronary inflow. Finally, occlusion of both the coronary sinus and all grossly visible anterior cardiac veins reduces inflow further, but the hearts generally survive and coronary inflow increases with increased load. Even with chronic ligation of the anterior cardiac veins and the coronary sinus, the peripheral coronary venous pressure returns toward normal within 30 days (153).

From these observations, it does not seem likely that a considerable elevation of right atrial pressure will influence significantly coronary inflow in the normal heart.

CORONARY ARTERIAL PRESSURE. The mechanisms concerned in alterations of coronary flow following acute elevation or depression of central coronary pressure have been only partially elucidated. Before considering the effect of coronary perfusion pressure on coronary flow, attention is called to the experimental

fact that in the presence of a declining coronary perfusion pressure, coronary flow ceases even when coronary perfusion pressure is still sizeable, an observation also made in the renal and mesenteric beds (150) (see values under Physical Determinants of Coronary Flow). Coronary inflow (right or left coronary artery) immediately increases throughout the cardiac cycle with a rising perfusion pressure and decreases with a falling perfusion pressure in all preparations studied.

In both right and left hearts, however, there is no set relationship between coronary flow and change in central coronary perfusion pressure, the effect on flow of a given pressure change varying from zero to a maximum. The degree of change and its duration will depend upon the extent of passive and active changes in resistance within the myocardium associated with the alteration of perfusion pressure. In the heart doing no external work (empty, beating, or fibrillating), the change in coronary flow is sizeable with moderate change in coronary perfusion pressure, but various relationships are observed. The resistance may be semilogarithmic (80, 283, 341), i.e., it decreases with increasing flow, or at the highest flow rates resistance may be constant or may increase. Associated changes in resistance in the coronary bed can be demonstrated when the vessels are perfused at various pressures with the cardiac work kept constant or not varying greatly. In the open-chest dog, there is a rapid and marked change in coronary flow within a few seconds following change of the perfusion pressure. The induced change in coronary flow may remain for some time (1 to 2 min) or it may return toward, to, above, or below the control flow level, thus showing large resistance changes in the coronary vascular bed (89, 158, 249, 315). A similar autoregulation of blood flow in the presence of a mechanically induced change in perfusion pressure has been observed in other regions such as the kidney (363) and skeletal muscle (353).

It is not surprising that in these various situations, most of which are highly abnormal, a variable relation of pressure to flow exists. It is believed that these changes represent automatic shifts in the size of the coronary vascular bed and in vascular resistance (passive and active blood vessel changes) which serve to meet the metabolic needs of the myocardium. Whether they are related to the oxygen supply and demand, to the relative amount of metabolites washed away, or to some other control, is not known.

One of the largest changes in coronary flow from altered coronary perfusion pressure occurs during

aortic constriction with the heart beating and working in situ. In general, in such instances in which a change in coronary flow resulting from alteration of coronary perfusion pressure is associated with a change in ventricular stress (ventricular size or systolic pressure, or both), the coronary A-V oxygen is the same or increased slightly while the oxygen consumption changes considerably in the same direction as the flow. Since the heart rate (generally fast) does not alter greatly, both stroke coronary flow and stroke coronary oxygen usage show large increases.

The oxygen uptake of a heart in the open-chest dog performing external work can apparently be altered by changing abruptly or gradually the level of a constant coronary perfusion pressure by 5 to 35 mm Hg for periods up to several minutes. The apparent oxygen uptake of the left ventricle increases significantly when coronary perfusion pressure increases. When coronary perfusion pressure decreases, oxygen uptake decreases. This change in oxygen uptake by the myocardium associated with the opposite change in coronary A-V oxygen occurs in the presence of a constant arterial blood pressure, heart rate, stroke volume, and cardiac work. Similarly, in isolated hearts not performing external work, the change in coronary flow from alteration of coronary perfusion pressure is counterbalanced by a shift in the coronary A-V oxygen in the opposite direction, but the oxygen uptake is changed significantly especially at the higher levels of coronary perfusion pressure. As yet, experimental testing has not been able to ascribe this apparent change in oxygen uptake to an artifactual happening (158, and unpublished observations on the isolated heart). These findings, which have been confirmed (7), would seem to make suspect various observations, especially in the isolated heart, in which perfusion pressure has been varied.

Many observers have reported that a given increase in work of the heart, produced by raising aortic pressure (aortic clamp) while holding cardiac output constant, results in a much higher coronary flow and oxygen usage per minute and per beat than when a similar increase in cardiac work is effected by elevating cardiac output through increased venous return at a constant aortic blood pressure (208). This discrepancy between the relative oxygen costs of pressure and flow work is observed in the isolated heart as well as in the dog with a complete circulation. In experiments with the isolated, supported heart with a constant heart rate, an increase in left ventricular work, by augmenting cardiac output while at the same time lowering aortic pressure by aortic

clamp release, results in a large increase in cardiac work associated with a decrease in oxygen usage (334). These observations taken together stress the importance of the aortic pressure and of the development of tension by the heart in the control of oxygen utilization.

Chemical Composition of the Blood

The chemical composition of the blood and tissue fluids within the myocardium has been found to be of great importance in determining the volume of coronary flow.

ASPHYXIA. Asphyxia, in which the carbon dioxide content of the blood increases and the oxygen content decreases simultaneously from cessation of breathing, is accompanied by a large increase in coronary inflow in the anesthetized dog. Within 30 to 60 sec after cessation of respiration, the flow in both systole and diastole increases, averaging about 200 per cent, and this occurs before any significant change in aortic pressure or heart rate (147).

HYPOXIA. When the oxygen content of fully saturated arterial blood of normal hematocrit is decreased by exposing it to successive mixtures of oxygen and nitrogen, containing progressively less oxygen (100% O₂ down to 5% O₂), the resultant arterial hypoxia induces profound increases (200–300%) in coronary arterial inflow in both systole and diastole in the fibrillating heart, isolated heart, heart-lung preparation, and anesthetized dog, but the oxygen consumption is not changed (26, 113, 147, 167, 182). In the anesthetized dog, as the arterial oxygen saturation decreases, the coronary A-V oxygen difference and coronary sinus oxygen content are decreased as the oxygen extraction increases. For example, starting with a control coronary sinus oxygen content of 4.2 vol per cent and saturation of 20 per cent, the coronary A-V oxygen difference may be decreased to 3 vol per cent and the coronary sinus oxygen to 1 vol per cent, while the oxygen extraction may be increased to 95 per cent. Similar findings are reported in man (181). Eventually, heart rate, blood pressure, and cardiac output may be elevated, presumably from the marked increment of cardiac contractility arising from stimulation of the sympathetic nervous system (408) since anoxia has only a depressant effect on the completely isolated heart (242). The increase in coronary flow precedes any change in these parameters and maximal coronary dilatation

occurs when the arterial saturation falls to about 20 per cent of normal.

Since the flow effects of systemic anoxia produced by artificial respiration with air and nitrogen and of local myocardial anoxia by underperfusion or by cyanide injection (147) into the coronary artery are similar, it is concluded that they all depend upon the anoxia produced, and probably upon the presence of this anoxia in the myocardium. Since the blood pressure does not change and the ratio of pressure to flow increases throughout the cardiac cycle, it is also concluded that anoxia causes a relaxation of the walls of the coronary vessels. To what extent this is active, that is, a direct effect on smooth muscle of the coronary vessels, and to what extent, if any, extravascular support has been lowered, cannot be ascertained by these experiments. By using the technique already described of prolonged vagal stoppage of the heart for separation and fractionation of flow determinants, coronary perfusion with saturated blood has been compared to perfusion with somewhat unsaturated blood. The resulting flow increase in the beating heart, in the latter instance, is shown to be about equally divided between a decreased extravascular compression and an active vessel relaxation (158).

The ultimate cause of the decrease in coronary vascular resistance in the presence of hypoxemia is not known, but it could arise from a direct action of low arterial oxygen content of the blood on the smooth muscle of the coronary vessels (182) or from hypoxia of the myocardium. To differentiate these possibilities, open-chest experiments have been made on fibrillating dog hearts, involving coronary perfusions with blood at varying levels of saturation and at high perfusion pressures which increased the coronary flow until coronary sinus blood became relatively rich in oxygen (26). In the presence of a quite high coronary perfusion pressure, considerable lowering of arterial oxygen content (to 10 vol per cent) does not increase coronary flow. An increase in flow occurs only at coronary sinus oxygen levels less than 5.5 vol per cent. Since the coronary sinus oxygen content probably closely reflects tissue oxygen content, this finding suggests that arterial oxygen content is not critical in the regulation of coronary flow but that coronary vasodilation in hypoxemia is related to myocardial hypoxia (myocardial oxygen content). Finally, experiments are reported in which the coronary arteries of the isolated heart are perfused with a fully saturated hemoglobin solution whose oxygen content is varied by dilution. In this situation, as the

oxygen content was varied from 18 vol per cent down to 2 vol per cent by dilution with Ringer-Locke's solution, the coronary flow increased although the intravascular oxygen tension at the level of the arterioles was kept constant (164).

METABOLITES. The mechanism whereby hypoxia operates to increase coronary flow remains obscure. Presumably, metabolites accumulate but their nature and possible effectiveness are unknown. Experiments dealing with this problem in which an extracorporeal circulation of blood is used must be cautiously evaluated. Dog blood contains potent vasoconstrictor and vasodilator substances. The red cells, especially, contain a potent vasodilator substance (adenosine triphosphate). This and other substances are readily made active by hemolysis resulting from minute mechanical trauma and agitation (60). In the heart-lung preparation, coronary flow generally progressively increases as the experiment continues, and substances accumulating in the coronary venous blood were originally thought to cause vasodilatation when reinfused into the coronary arteries (17). Hilton & Eicholtz (182), however, could not confirm this in the isolated heart, for replacement of the blood that had circulated for some time by fresh defibrinated blood did not significantly alter flow.

It is not clear whether or not vasodilator substances exist in the coronary sinus blood of the heart beating within the chest in sufficient concentration to alter coronary blood flow. In recent experiments, blood draining normal, hypoxic, or overperfused (perfusion pressure considerably greater than aortic pressure) hearts has been oxygenated in a dog lung or on a screen and perfused at a controlled pressure through a rotameter into a test coronary artery of the same or second dog, or unoxygenated coronary sinus blood has been perfused into an isolated beating frog heart. These experiments have failed to demonstrate substances having vasoactive, inotropic, or chronotropic properties in the coronary sinus blood (193). On the other hand, injection of coronary sinus blood obtained during cardiac sympathetic nerve stimulation causes a moderate coronary dilatation at the same blood pressure and heart rate (277).

Intracoronary injection of intermediate metabolites will increase coronary blood flow. Histamine, metabolites such as adenosine, adenylic acid, and breakdown products of nucleic acids increase coronary flow in the perfused heart, the human heart-lung preparation and heart *in situ* (10, 277). However, it has never been demonstrated that the concentration of these sub-

stances increases within the myocardium during anoxia or increased effort of the heart. Studies on relative coronary vasodilator potency show that adenine is relatively inactive, while adenosine triphosphate and adenosine diphosphate have approximately four times the potency of adenosine monophosphate, adenosine, and uridine triphosphate (406, 407). In addition to vasodilator properties, some of the purine and pyrimidine derivatives have been demonstrated to have positive inotropic action in the normal and failing heart (52). It is not surprising, therefore, that in the open-chest dog with constant pressure perfusion of the coronary arteries, some of these substances (ATP and UTP) with inotropic and vasodilator properties also increase the myocardial oxygen consumption (407). However, since the elevation in coronary blood flow is greater than that necessary to meet the increased oxygen demand, i.e., the coronary A-V oxygen is decreased considerably, the action of such compounds is probably largely on the coronary vessels, and only secondarily on metabolic rate.

Although it has not been possible to demonstrate in the coronary sinus blood substances having vasoactive, chronotropic, or inotropic properties, this does not necessarily rule out an active role of metabolites in regulating coronary flow. As pointed out by Berne (28), although adenosine and adenine nucleotides are not recoverable in the coronary sinus, derivatives of adenosine such as inosine and hypoxanthine appear in the coronary sinus blood during periods of myocardial hypoxia, and vasoactive concentrations of adenosine added to coronary arterial blood are recoverable in the coronary sinus only as inosine and hypoxanthine. Thus, the possibility should be entertained that in hypoxia, myocardial nucleotides give rise to adenosine which diffuses out of cardiac cells, induces vasodilatation, but is deaminated and split before separation from the blood can be effected.

ACIDOSIS AND ALKALOSIS. In the isolated heart or heart-lung preparation, acidosis induced by administering CO₂ or lactic acid dilates the coronary blood vessels, for coronary flow may increase (182) despite a marked reduction in the rate, output, arterial blood pressure, and contractile force of the myocardium (273). In an intact preparation in the presence of severe respiratory acidosis (from CO₂ administration), or a fixed acidosis (from infusion of HCl solution), coronary flow increases (114), remains constant (134), or decreases (90, 147), while systemic dynamics (blood pressure, heart rate, and cardiac output) are not largely

changed. In contrast to its direct depressant effect on the isolated perfused heart, a CO_2 concentration in the respired air of the open-chest dog of at least 8 per cent has a stimulating influence on the myocardium for the contractile force may not be lowered and myocardial function curves are not depressed (267). Presumably, this arises from its stimulating influence on the sympatho-adrenal system since acidotic heart failure in the heart-lung preparation can be reversed by administration of sympathomimetic amines. The divergent results with hypercapnia may, therefore, merely express the variable weighting of the antagonistic effects on the intact animal circulation, of a direct depressant effect on the myocardium and smooth muscle of the coronary vessels, and of an indirect stimulating effect on the same structures through the sympatho-adrenal system. In the intact dog, hypocapnia (arterial CO_2 less than 35 vol per cent) is without effect on systemic and coronary hemodynamics and the ventricular function curve is unaltered (114, 267).

In the isolated heart doing no work, alkalosis induced by varying the bicarbonate concentration of the perfusing solution, or following CO_2 administration, depresses inotropic and chronotropic cardiac activities but increases coronary flow. These changes in cardiac function are effected only when the pH of the perfusate is altered (248). Sodium bicarbonate infusion in the intact anesthetized dog stimulates both systemic and coronary hemodynamics. In the presence of an essentially constant heart rate and arterial blood pressure, and a marked increase in cardiac output, the coronary flow and oxygen usage per minute and per heart beat are elevated considerably (134). The mechanisms concerned are not known. Nor has it been established whether these effects of acidosis and alkalosis on the coronary circulation in the intact dog arise from changes in pCO_2 , HCO_3 , or from the resulting change in pH, since in no instance has the pH been separately controlled.

POTASSIUM, CALCIUM. There has not been sufficient experimentation to determine the role, if any, of the electrolytes in regulating the coronary circulation. Increased potassium concentration (150%) in the blood perfusing the fibrillating heart of the Langendorff preparation increases coronary flow, while larger intracoronary concentrations in the open-chest dog also produce similar increases (88). In the heart-lung preparation, isolated heart, or heart within the chest, very large potassium concentrations sufficient to arrest the heart reduce coronary inflow (249,

259). In the latter instance, the oxygen usage is also greatly reduced as a result of a decreased flow and oxygen extraction. In the open-chest dog, upon the addition of pharmacological amounts of Ca gluconate, coronary flow and oxygen consumption increase and oxygen extraction decreases without much change in blood pressure and heart rate (115).

Transfusion

Augmentation of ventricular load by increasing venous return, and, hence, circulating blood volume through infusion has a clinical counterpart in the load placed upon the human heart by transfusion or by an aortacaval fistula. During transfusion, systolic and diastolic heart size, ventricular stroke volume and stroke work, atrial and ventricular end-diastolic pressures and arterial blood pressure all increase as the heart rate slows considerably. When the coronary arteries are perfused at a constant pressure or with a normal pulsatile aortic pressure, an increase in the cardiac output or cardiac work through augmentation of venous return to the heart beating in situ augments moderately the coronary flow and oxygen usage per minute and per heart beat while the aortic pressure rises (46, 90, 152, 153). The increasing coronary flow is partially explainable on a mechanical basis since the slowing of the heart should increase coronary flow per beat and per minute by increasing the diastolic time period during which coronary flow is greater. The coronary flow and oxygen are used economically, for the ratio of stroke cardiac work to stroke oxygen consumption increases. However, it has been repeatedly shown in the denervated heart and heart-lung preparation that coronary arterial inflow and coronary sinus outflow are reduced somewhat or unchanged by alterations in cardiac output as long as the resistance against which the ventricles contract is unaltered (10). These findings have been extended to the open-chest dog in which coronary flow and oxygen usage may not change or may rise only slightly in the presence of a constant arterial blood pressure and marked increase in cardiac output (46). In the isolated supported heart, the coronary flow and oxygen usage per minute and per heart beat can be made to decrease in response to a lowering of arterial blood pressure, achieved by release of an aortic constriction during the augmentation of cardiac output which follows an increase in venous return (334).

Since the average individual is transfused only on rare occasions, it is not known whether such informa-

tion can be used to explain happenings in the coronary circulation of the normal heart exposed to the stresses of everyday life. At least, in the latter instance the systemic dynamics are quite different from those listed above as occurring with transfusion. For example, in exercise and excitement, while the heart rate increases greatly and the duration of systole decreases, cardiac size may decrease and stroke volume and atrial and ventricular diastolic pressures may undergo only limited changes.

Anemia

The coronary system participates actively in the circulatory adjustments to anemia. For hemoglobin values of 10 g or more, the systemic circulation is essentially unaltered and the compensation of the coronary system to the decreased oxygen-carrying capacity is similar to that with hypoxia, i.e., an increased coronary flow without change in oxygen uptake. When the hemoglobin values reach 6 to 8 g, the response of the systemic circulation is manifested by tachycardia, increased cardiac output and cardiac work, and a fall in peripheral resistance. The coronary flow may now triple; coronary venous blood may contain less than 2 vol per cent oxygen, the coronary arteriovenous oxygen difference may be 4 ml or less, and oxygen uptake may be considerably increased. The increase in coronary flow is related in part to the decreased blood viscosity, and in larger part to the active dilatation associated with myocardial hypoxia, which in turn arises from the low hematocrit and from the increased metabolism. Ultimately, myocardial failure will occur in severe anemia when the coronary vessels have approached maximal dilatation and cannot further compensate for the decreased oxygen-carrying capacity of the blood either by increased flow or by increased oxygen extraction. In the presence of coronary stenosis associated with anemia, the effect of coronary arteriolar dilatation in increasing flow is minimized by the high fixed resistance of the stenotic artery, and myocardial depression and failure occur at lesser degrees of anemia (31, 57).

Very little information is available regarding the coronary circulation in the presence of polycythemia vera. The expanded red cell mass has been associated with a considerable reduction in coronary blood flow and an increased oxygen extraction without change in oxygen usage. Allocation of these changes to an enhanced oxygen-carrying capacity or to a viscosity effect has not been made (305).

Nervous Influences

The control of the coronary circulation by parasympathetic and sympathetic nerves has been the subject of intensive investigation and dispute. Many experiments, however, have been interpreted with difficulty since cardiac output and cardiac work were not determined, and heart rate and arterial blood pressure which affect coronary flow and oxygen usage varied widely (90, 187, 340, 405). There is some evidence to indicate that the over-all nature and extent of neural cardiogenic control is some degree of coronary vasoconstriction since *a*) an outstanding characteristic of the isolated heart or heart-lung preparation is a very high coronary blood flow and low myocardial oxygen extraction, and *b*) in chronic dogs the procedure of pericoronary denervation results in a relative increase in coronary flow and decrease in oxygen extraction (43). For the most part, the nervous system influences on the coronary circulation have been studied by observing the coronary flow, oxygen usage, and contractility responses following electrical stimulation or severance of the nerves. Although such procedures are not paralleled by normal occurrences in the animal, the observed responses are presumed to indicate the functions which the nerves are capable of exercising in the intact animal. Further difficulty in interpretation arises from the fact that the specific effects upon the heart muscle and on the coronary vascular system are largely experimentally inseparable and only the net effect can be observed. Differences in methods and preparations are additional variables which may account for the discordant results of different investigators.

VAGUS. Recent studies of the effect of the vagus nerves on the heart have gradually clarified our view of their effect on the coronary circulation. Early evidence indicated that the vagus nerves contain both dilator and constrictor fibers (401). That the vagus exerts a vasoconstrictor effect is based on observations that abolition of the parasympathetic pathways in the heart-lung preparation (by mechanical and chemical means) results in augmentation of heart rate or coronary flow, while stimulation of the peripheral ends of the cut vagi decreases coronary flow (10). The evidence that it exerts a vasodilator effect arises from the observation that in the fibrillating heart with coronary arteries perfused with blood under a constant pressure, vagal section usually decreases coronary inflow but vagal stimulation usually increases

coronary inflow (206). It would seem unlikely that the vagus would act as a vasoconstrictor since its chemical transmitter, acetylcholine, is a coronary vasodilator.

Such studies, of course, do not define the action of the vagi in the intact animal. In the open-chest dog with the heart rate maintained at a constant value by an electric pacemaker, section of these nerves or stimulation of their cut ends does not usually evoke significant change in coronary inflow, coronary sinus flow (orifice meter, bubble flowmeter, rotameter), or in coronary A-V oxygen difference, while blood pressure and cardiac output are essentially unchanged (83, 90, 236, 339). In all preparations, ventricular contractility is usually not changed (367). These observations are in accord with the apparent lack of vagal fiber distribution to the ventricular myocardium (54, 262). At times, vagal stimulation (378) has been observed to cause reduction in cardiac output, blood pressure, and coronary inflow, an effect which was abolished by atropine. Although this effect is ascribed by the authors to a negative inotropic effect of vagal stimulation on the ventricular muscle, it could also have resulted from diminution of vigor of atrial contraction thus reducing ventricular filling, a finding of different investigators (336).

SYMPATHETIC. Stimulation of the stellate ganglion or its cardiac branches in the anesthetized open-chest dog or in the unanesthetized resting dog increases mean flow in both right and left coronary arteries (83, 139, 153). This augmentation lasts for minutes and persists long after any augmentation of heart rate or blood pressure (if such occurs) has returned to normal. Figure 9 is a response of the left circumflex flow obtained with an electromagnetic flowmeter in a resting unanesthetized dog a few days after probe implantation. In this dog, in which the left stellate ganglion had been previously disconnected from the thoracic sympathetic chain and spinal nerves to eliminate peripheral effects of excitation, stimulation of the common ansa subclavia initially and transiently decreases coronary flow throughout the cardiac cycle without change in blood pressure or heart rate. Within a few seconds, at an unchanged blood pressure but increased heart rate, mean coronary flow increases as the result of an increase in diastolic flow and in spite of a depression of systolic flow with appearance of backflow. Almost immediately, thereafter, coronary flow increases greatly throughout the entire cardiac cycle, with the disappearance of backflow. This pattern of response to stellate stimulation may occur with or without spontaneous elevation of blood pres-

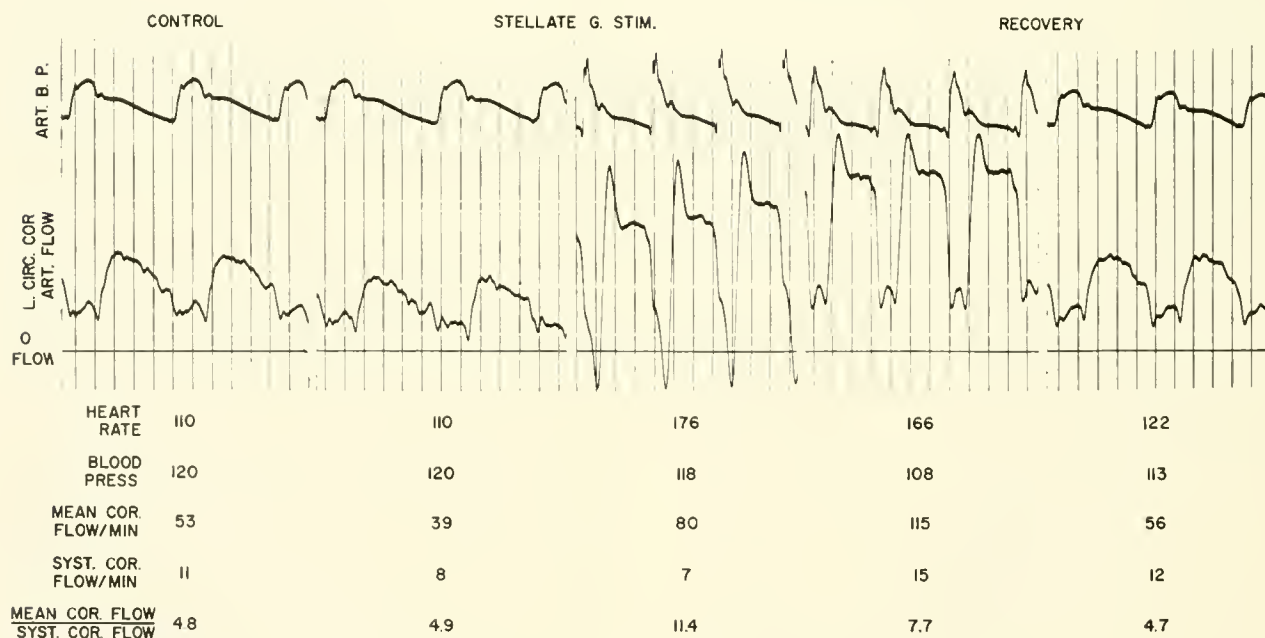


FIG. 9. Reproduction of sections from a continuous record in a conscious dog a few days postoperative, showing effect of left stellate ganglion stimulation on phasic arterial blood pressure and stroke left circumflex coronary inflow using a strain gauge and electromagnetic flowmeter as in fig. 6. Connections of stellate to sympathetic chain severed at time of operation. [Granata *et al.* (139).]

sure and heart rate, or when the aortic blood pressure (in open-chest dogs) is artificially controlled and compensated to the control level. This indicates that the factors of heart rate, blood pressure, and work are not indispensable to the natural mechanism through which the flow increase is mediated. The major portion of the flow increase is related to active dilatation since blood pressure does not necessarily rise. The net flow increase rests in part, however, on a mechanical basis, for the duration of systole (in which flow is less than in diastole) is reduced and thus, at the same heart rate, the period of time occupied by diastole (in which rate of flow is greater), is increased considerably. About 30 per cent of the flow increase is estimated to be due to this shortening of systolic and lengthening of diastolic time per beat or per minute (93). Concurrently, left ventricular oxygen usage, cardiac output, and cardiac work, either per minute or per heart beat, increase while the systolic and diastolic dimensions of the heart decrease. Since the blood pressure and heart rate do not necessarily change during the flow increase, while duration of systole shortens, the stroke coronary flow does not correlate with pressures developed by the ventricle or with directional trends in ventricular tension calculated thereon.

The evidence is well founded that stimulation of the sympathetic nerves to the heart aids greatly in maintaining and augmenting the rate and contractility of the heart, as shown by improvement in the atrial and ventricular function curves from any given atrial, ventricular end-diastolic pressure (263, 336), or fiber length, and in the gradient of the aortic pressure and stroke volume curves (11, 153, 211). In no experiment has coronary inflow been found to increase without experimental evidence of increased vigor of contraction, increased cardiac work, and metabolism. The mechanism by which this is accomplished has not been completely identified. The possibility that adrenal secretion is responsible for the cardiac stimulating effect has been largely discounted experimentally (153). The facts that *a*) administration of acetylcholine to an atropinized heart results in liberation of an adrenaline-like substance (186); *b*) that this substance is also normally present in heart extracts (376); and *c*) that stimulation of cardiogenic sympathetic fibers sets free an adrenaline-like substance (284, 346), all support the view that a dominant role is played by myocardial catecholamines.

The experiments of Eckstein *et al.* (93) offer evidence that this process is very wasteful, for the increase in the work of the heart is not essential to the asso-

ciated increase in coronary inflow. Stimulation of the accelerator nerves in the open-chest dog produces an increase in vigor of contraction, cardiac output, cardiac work, coronary blood flow, and oxygen consumption. However, simultaneous nerve stimulation and inflation of a left auricular balloon to reduce the external work of the heart below the control value is likewise followed by increased vigor of contraction, increased coronary flow and increased oxygen consumption. Thus, the adrenaline-like substance released by nerve stimulation would appear to increase oxygen consumption directly.

The preceding observations do not preclude the possibility that the major influence of the sympathetic cardiac nerves may be to exert a direct vasomotor influence on the coronary vessels, the initial temporary coronary vasoconstriction which invariably occurs being overpowered by metabolic dilator influences associated with the type of stimulation. It is, however, most difficult to establish and identify conclusively, by experimental means, the separate effects of nervous influences upon the myocardium and coronary vessels because the physiological functions of these structures are so intimately related that their individual responses can be secondarily modified, each by the other. In the innervated fibrillating heart, stellate stimulation at times decreases coronary flow, while nerve section increases coronary flow (206). Recent evidence indicates the existence and functional importance of coronary vasomotor fibers the action of which in previous investigations was presumably obscured because of a nonselective type of nerve stimulation (199, 358). As other workers have shown, excitation of high threshold postganglionic (stellate or inferior cervical) cardiosympathetic fibers with high voltage and high frequency stimulation causes profound alterations in myocardial metabolism which could not be prevented by ergotamine or atropine. However, appropriate stimulation of preganglionic fibers, using low voltage and low frequency, leads either to coronary vasoconstriction (decreased coronary flow and blood pressure and increased coronary A-V oxygen without alteration in oxygen consumption), or to coronary vasodilation (increased coronary flow, decreased coronary A-V oxygen without blood pressure elevation and without alteration in cardiac metabolism). The magnitude and importance of these direct vasomotor effects remain to be determined. In the author's laboratory, preliminary attempts have failed to demonstrate these direct vasomotor influences of the cardiac sympathetic fibers in the unanesthe-

tized dog with a chronically implanted electromagnetic flowmeter on the coronary artery.

To the author's knowledge, the existence of a tonic action on the coronary circulation of the intact animal, attributable to the parasympathetic and sympathetic nerve fibers, has never been demonstrated, the section of these nerves in the open-chest dog leading only to nonspecific changes. Study of this problem should be made through the application to the coronary circulation of recent techniques for coronary neurectomy and extrinsic cardiac denervation on chronic dogs (43, 71).

REFLEX CONTROL. Our knowledge of the role of the central nervous system in regulation of the coronary circulation in health and disease is sufficient to warrant discussion but is certainly insufficient to draw firm conclusions. This arises from a lack of proper experiments in which studies of both the reflexes and the coronary hemodynamic responses have been simultaneously made. A proper demonstration depends on the observations that the vagus and sympathetic nerves to the heart are tonically active as far as coronary blood flow regulation is concerned, or can be made so by the induction of adequate stimuli arising either within the heart or peripherally.

Different observations support the view that there are receptors in the distribution of the canine left coronary artery. Injection of veratridine into a left coronary artery (but not the right coronary), going only to the left ventricular muscle and in amounts insufficient to affect the systemic circulation upon direct injection into the left ventricle, causes an abrupt fall in blood pressure and heart rate (76, 77). Circulatory depression which may follow selective augmentation of central coronary pressure near the left coronary orifice and the initial part of the descendens artery, or which may occur during coronary sinus occlusion, is relieved by vagal section (132, 187, 285).

The evidence is equivocal that flow in one coronary artery can be influenced reflexively and adversely by impulses arising in another occluded coronary artery. Various supportive observations suggest that noxious intercoronary reflexes can be made to occur: *a*) Ligation of a coronary artery is stated to cause reflex spasm or vasoconstriction in the other coronary artery resulting in fatal ventricular fibrillation (231). This is presumed to be abolished by bilateral vagosympathetic blockade (228). The infarction after coronary ligation is increased with vagal stimulation and is prevented by local anesthesia of the vessel wall at the

site of the ligature (220, 223). *b*) In the anesthetized closed-chest dog with visualization of the coronary artery bed by cinefluorography after injection of a radiopaque dye, selective embolization (lycopodium spores) of a coronary artery branch results in a marked decrease in size of the nonembolized coronary artery bed and in coronary sinus flow (165). On the other hand, *a*) West *et al.* (392), using techniques similar to those of Guzman, failed to find evidence of reflex coronary vasoconstriction following coronary embolization. *b*) In the open-chest dog, following ligation of the right or left coronary artery, the coronary flow (rotameter) rises and resistance falls in the unoccluded coronary artery, such flow augmentation presumably resulting from an anatomical and functional overlap of the right and left coronary arteries (153, 282, 377). *c*) In the unanesthetized resting dog, some days after implantation of an electromagnetic flowmeter on the main left coronary artery or a major arterial branch, temporary (10–30 sec) occlusion of a left coronary artery branch results either in no change or an increase in blood flow in the artery in which flow is being measured (L. C. Fisher, unpublished observations). It must be remembered that these experiments with negative results follow considerable dissection of the coronary arteries, and actually represent conditions which deviate extensively from the normal nerve state. Thus they do not rule out the possibility of reflex coronary vasoconstriction occurring in small localized regions of the myocardium after coronary occlusion.

Changes in coronary blood flow which might result from extracardiac stimuli would be of great clinical interest, and their demonstration might aid in elucidating the mechanism of the relationship between angina pectoris and its various incitants, such as eating, abdominal distention, cold, and exercise. The claim is made that many diverse afferent stimuli affect the coronary circulation. Prolonged experimental neurosis in monkeys produced by conflicting conditioned reflexes or selected brain stimulation can produce ECG changes identical to those of human ventricular ischemia (250). Stimulation of many afferent nerves, distention of the stomach, gall bladder and esophagus, and cutaneous pain, all are presumed to decrease coronary flow in the anesthetized dog, while elevation of cerebral blood pressure and carotid sinus pressure decreases coronary flow in the innervated heart-lung preparation (blood pressure and heart rate kept constant) (153). In these experiments, the recording devices and data were generally insufficient to establish that no changes occurred in

heart rate, cardiac output, blood pressure, length of systole and diastole, each of which could alter cardiac metabolism, work and coronary flow separately or in combination. Actually, in experiments with adequate flow methods, *a*) increase in intragastric or intrabiliary tension gives a variable flow response (bubble flowmeter and rotameter) but always in the same direction as the blood pressure change (90, 285, 405); *b*) dermal contact with ice water in the anesthetized dog fails to produce reflex constriction of the coronary arteries (24, 347). The sight, smell, and ingestion of food and tilting the head down all increase coronary flow (electromagnetic flowmeter) concurrently with an augmented heart rate and blood pressure (301). It is therefore unreasonable to maintain, as has been done, that such agents have caused active vasoconstriction or vasodilatation in the coronary bed and that such changes are necessarily largely controlled through nervous reflexes. This is especially so since in each experiment the effects of the stimuli were not generally tested after as well as before the cutting of the cardiac nerves.

Thus, while reflexes to the coronary circulation from

the heart or extracardiac visceral structures certainly do exist and may be important in normal physiology and pathological physiology, we must wait for the future to show their exact function.

Hormones

NOREPINEPHRINE AND EPINEPHRINE. Since the generally accepted theory of autonomic nerve transmission is based on the liberation of acetylcholine and epinephrine-like substances, the coronary flow effects with these agents are of particular interest in connection with coronary innervation.

The action of epinephrine on the coronary blood flow has been investigated extensively. In most dog preparations, including the fibrillating heart (27), heart-lung preparation (179), the open-chest dog (82, 83, 112, 146), and the unanesthetized dog a few days postoperative to flowmeter implantation (301), intracoronary artery injection of epinephrine and norepinephrine increases coronary blood flow. In the latter two preparations, their effect on the coro-

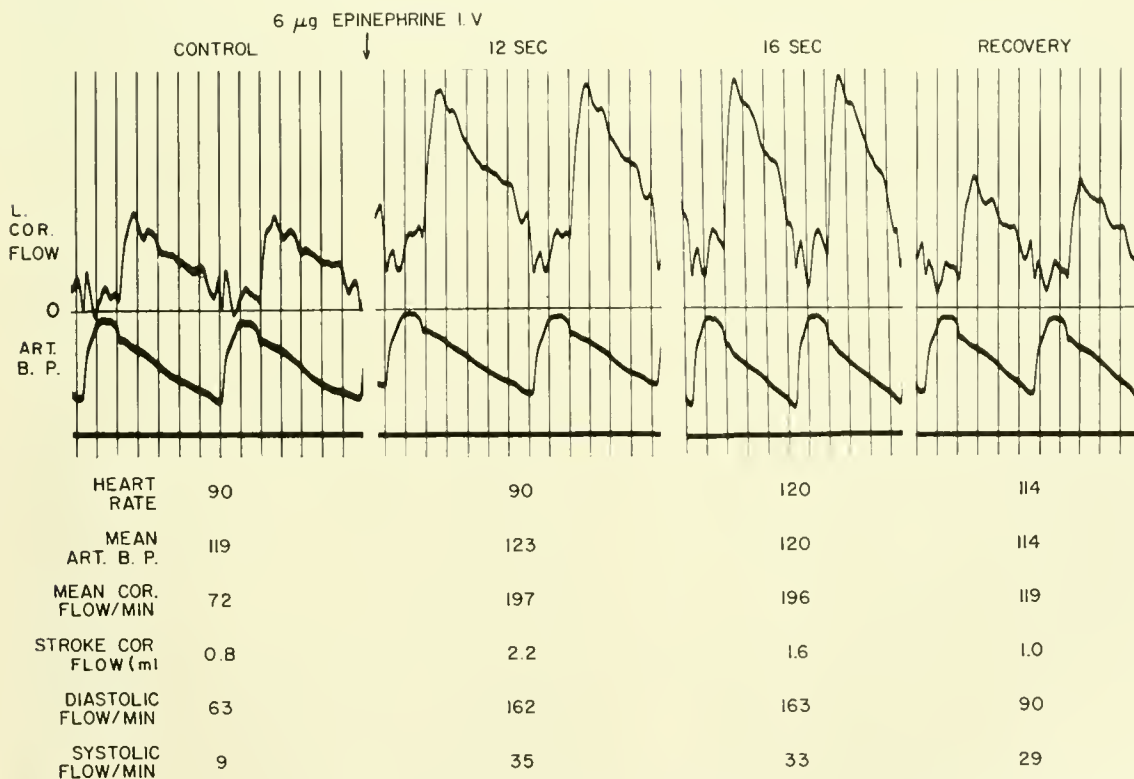


FIG. 10. Reproduction of sections from original record taken in a conscious resting dog some days postoperative, showing the effect of rapid intravenous injection of 6 µg epinephrine on phasic arterial blood pressure and stroke left circumflex flow, using a strain gauge and electromagnetic flowmeter as in fig. 6. [Rayford *et al.* (301).]

nary flow pattern is similar to the sustained effect obtained during stimulation of cardiac accelerator nerves, i.e., an increased blood flow throughout the cycle (fig. 10). In all animal preparations, as well as in man, myocardial contractility is increased to a marked degree as indicated by the intensity of fibrillatory movements in the fibrillating heart, by depression of the isometric and systolic portions of the phasic inflow curve in the dog, and by an increase in myocardial contractile force as measured by a strain gauge arch in man and animal (131). Both intravenous and intracoronary artery injections increase cardiac oxygen consumption, in the first instance by increasing coronary flow and decreasing coronary A-V oxygen difference (112), in the second instance by increasing coronary flow and increasing coronary A-V oxygen difference (27). This occurs even in the vagus-stopped heart (249). With very small doses, coronary inflow may increase without any change in blood pressure or heart rate and with increased coronary A-V oxygen difference. With larger doses, as the systemic effects of the substance (increased aortic blood pressure, cardiac output, and changing heart rate) become evident, the coronary and metabolic effects are exaggerated (90).

From the preceding it can be seen that there is general agreement that these substances produce coronary vasodilatation. The flow increase is the net result of an augmented extravascular support tending to decrease coronary flow, a metabolic dilator effect tending to increase coronary flow and any direct effect the compounds may have on the coronary vessels. There is, however, disagreement and confusion regarding the respective magnitude of each separate effect. There is little doubt that with the larger doses, most of the flow increase is due to the large increase in myocardial metabolism. However, one point of view has it that these substances are primarily coronary vasoconstrictors, their vasodilator action arising secondarily from a hypoxic state of the myocardium as a result of their stimulating effect on the myocardial metabolism. The evidence for this is that epinephrine causes an initial and transient decrease in coronary flow in the fibrillating heart and in the beating heart (as does cardiac sympathetic nerve stimulation). Elevation of extravascular support as a cause of the early impediment to flow here apparently does not occur since intramyocardial pressure does not rise in the fibrillating heart (27), and extravascular resistance falls somewhat in the vagus-stopped heart (236). Unfortunately, since the duration of the period of constriction is so fleeting and the flow effect so mild, the view is very difficult to document.

ACETYLCHOLINE. Acetylcholine, intra-arterially, increases coronary blood flow in the dog in the fibrillating heart and in the heart-lung preparation (10). In the open-chest dog, intravenous injection of acetylcholine decreases aortic pressure and coronary flow, and increases heart rate as a result of a decreased systemic peripheral resistance (339). Intracoronary artery injection of effective doses of this hormone, and also intravenous injection (provided the blood pressure is mechanically compensated by an aortic clamp and the heart electrically driven following surgical induction of an A-V heart block), increases considerably left coronary inflow and coronary sinus flow, and decreases the left ventricular function curve (90, 339, 405). If the intracoronary dose is properly chosen, this response occurs without a significant effect on the systolic blood pressure, heart rate, systolic/diastolic time interval, cardiac output, cardiac work, but the myocardial oxygen consumption per minute and per heart beat increases. The increased coronary flow is completely abolished by atropine (405). Since the mechanical and metabolic factors which could influence coronary flow are thus excluded, the increase in coronary flow represents a true coronary vasodilatation (see fig. 13). The relation between myocardial oxygen consumption and left ventricular work is not changed. Consequently, the induced depression of myocardial contractility or work per unit of filling pressure is not associated with any change in myocardial efficiency (work per unit of oxygen consumption).

THYROID. The myocardium participates in the increase in oxygen consumption characteristic of all body tissues in thyrotoxicosis (398). This hypermetabolism is accompanied by an increase in coronary blood flow, a decrease in coronary vascular resistance, and an increase in oxygen consumption per minute and per beat. Since there is an increase in oxygen usage per beat, cardiac oxygen utilization is presumably related not only to the increase in heart rate but to the general hypermetabolism of the myocardium as well (230, 317).

Hypothyroidism in man has been shown to be associated with a reduction in heart rate, cardiac output, arterial blood pressure, and body oxygen usage. In vitro studies of experimentally induced hypothyroidism have demonstrated a reduction in oxygen consumption of the myocardium (130). Controlled experimental inactivation of the thyroid by use of I^{131} in the dog leads to standardized changes in the systemic circulation (342). In addition, coronary sinus flow (N_2O method) and left ventricular oxygen

consumption are reduced. Atropine raises each of these parameters (as well as the heart rate) to normal. These experiments are difficult to interpret. However, since the stroke coronary flow and stroke coronary oxygen usage are unaffected by hypothyroidism, the reduced flow and oxygen consumption are probably related in part to the altered myocardial metabolism.

PITRESSIN. There is agreement that Pitressin increases resistance to flow in the coronary circulation (146, 153, 218, 384). In the revived human heart perfused by the Langendorff method, and in the perfused dog heart in ventricular fibrillation, Pitressin decreases coronary flow. In the open- (146) or closed-chest dog, coronary inflow decreases, the reduction occurring throughout the cardiac cycle in the presence of an increased central coronary pressure and, sometimes, a mild reduction in heart rate. Selective angiography demonstrates visible vasoconstriction of the superficial coronary arterial tree (see fig. 13) (393). Although it seems reasonably sure that this hormone decreases coronary flow by a direct constrictive action on the coronary bed, simultaneous studies have not been made of the associated work and metabolism, and the possibility of a reduced metabolic influence has not been ruled out. If Pitressin has a direct action on the coronary vessels, presumably it acts at the arteriolar level. This is so since in the isolated perfused rabbit heart (176) Pitressin does not change the intracellular and extracellular Na and K values. If resistance increased at the venules or distal end of the capillaries, one might expect an increase in the extravascular space.

Exercise and Excitement

Most of the information thus far considered is based upon observations obtained from the resting human and the anesthetized, open-chest dog. It is not known to what extent it applies to normal situations, since the information has been obtained either under conditions far removed from normal, as the result of insults from anesthesia, surgery, and trauma in the last situation, and hence, it does not contain information from normal humans and animals as to the regulation of the coronary circulation exposed to the stresses of everyday life such as exercise, excitement, and positional changes. For example, in exercise and excitement, the heart rate is greatly increased. It is disturbing that in only two of all the conditions of stress in which heart rate increases, in the open-chest dog, do the stroke coronary flow and stroke coronary oxygen increase. These are in thyrotoxicosis

and with cardiac sympathetic nerve stimulation. In the others, stroke coronary flow and stroke coronary oxygen decrease. This would mean that coronary flow and oxygen usage are completely limited by the heart rate. For example, if the heart rate is tripled, coronary flow can only be increased three times. It is difficult to conceive that the heart works in this way, but rather that additional mechanisms can also increase the coronary flow per heart beat.

Accordingly, considerable effort has been expended to make appropriate measurements in the normal state. It is not to be expected that new parameters of control will necessarily exist in these stresses imposed by everyday life, but it is possible that their weighting will be quite different. Early observations indicated that in man (240) and in the dog (105) left coronary flow and myocardial oxygen consumption increased, while the coronary arteriovenous oxygen showed little change. More recently, an appropriate flowmeter has been applied to the coronary system of an essentially normal animal. Initially, it was believed that no flowmeter would operate properly if applied directly to the ventricle on the surface of the heart because of its violent motion. Therefore, in large dogs a systemic artery, either the carotid or internal mammary, was anastomosed by a nonsuture technique to the left circumflex coronary artery branch so that a flowmeter could later be mounted on it in a quiescent region off the surface of the heart. Angiograms and postmortem examination of the hearts indicated the patency of the anastomoses and the normalcy of the other coronary vessels and the myocardium. Of 33 dogs, 6 died of technical errors on the table or shortly thereafter, 3 died of thrombosis at the site of the anastomosis, 2 to 13 days postoperative. The remaining 24 dogs were sacrificed 12 to 24 months later. Prior to sacrifice an electromagnetic flowmeter, modeled after that of Kolin (217), was placed on the anastomosed internal mammary artery and the coronary blood flow measured daily for periods up to 2 months. Zero blood flow was obtained when desired by temporarily occluding the flow by means of a special rubber pneumatic cuff placed around the internal mammary artery just distal to the flow transducer at the time of its implantation (171).

These preliminary experiments in 1958 were encouraging. Electromagnetic flowmeters of the sine-wave type, but greatly modified and improved from the standpoint of miniaturization, sensitivity, stability, and ruggedness, were constructed (212a). The flow probes used on the left coronary artery were necessarily somewhat smaller than an aspirin tablet,

since the maximum space available for implantation on the main left coronary approximates 2 to 2.5 mm. A large electromagnetic flowmeter implanted on the ascending aorta (or pulmonary artery) gave simultaneous cardiac output per heartbeat. For phasic arterial pressure a plastic tube filled with heparin was implanted in the aorta just beyond the aortic flow transducer.

Strips of record in figure 11 illustrate the flow through the left circumflex artery anastomosed to the internal mammary artery in a large greyhound at standing rest, and running on a treadmill at 12 mph on a 5 per cent grade for 3 min (mild to moderate exercise for such a dog). As the heart rate almost triples, the mean coronary flow also triples. Despite this, stroke coronary flow does not increase but decreases mildly. The fact that the stroke coronary flow did not increase with exercise cannot be ascribed to increased resistance through the much longer anastomosed circuit because tests in acute experiments showed that coronary flow was the same in the long and short circuits up to levels of about 650 ml per min (344). Similar flow changes during exercise occur in the main left coronary artery and in the descendens and circumflex branches without anastomosis (212). This suggests that the coronary flow is limited by the heart rate. It is expected (as yet without proof) that with quite heavy exercise, the coronary flow per heart beat will rise.

The coronary flow response to varying degrees of excitement is quite different from that to exercise. In the experiment illustrated (fig. 12), a dog at rest underwent spontaneous excitement. As the heart rate increases from 98 to 250 beats per min, but without change in mean blood pressure, the left circumflex coronary flow increases from 94 to 344 ml per min, and despite the shortened diastole during which most of the coronary flow occurs, the coronary flow is more than tripled. In contrast to the response in exercise, however, stroke coronary flow increases from 1.0 to 1.3, this occurring during systole and diastole. Later, as a moderate increase in blood pressure occurs, the stroke coronary flow is approximately tripled. Similar flow responses to excitement have been observed in the main left coronary artery with or without a large blood pressure change. These experiments indicate that the heart is able to obtain an increased coronary flow during excitement not only because of the increased number of heartbeats, but also because of an increased flow per heartbeat.

Valvular Disease

It is difficult, if not impossible, to duplicate human valvular disorders experimentally because of lack of methodologies to assess accurately the degree of insufficiency and stenosis in both man and beast, to measure the coronary blood flow, and to make the

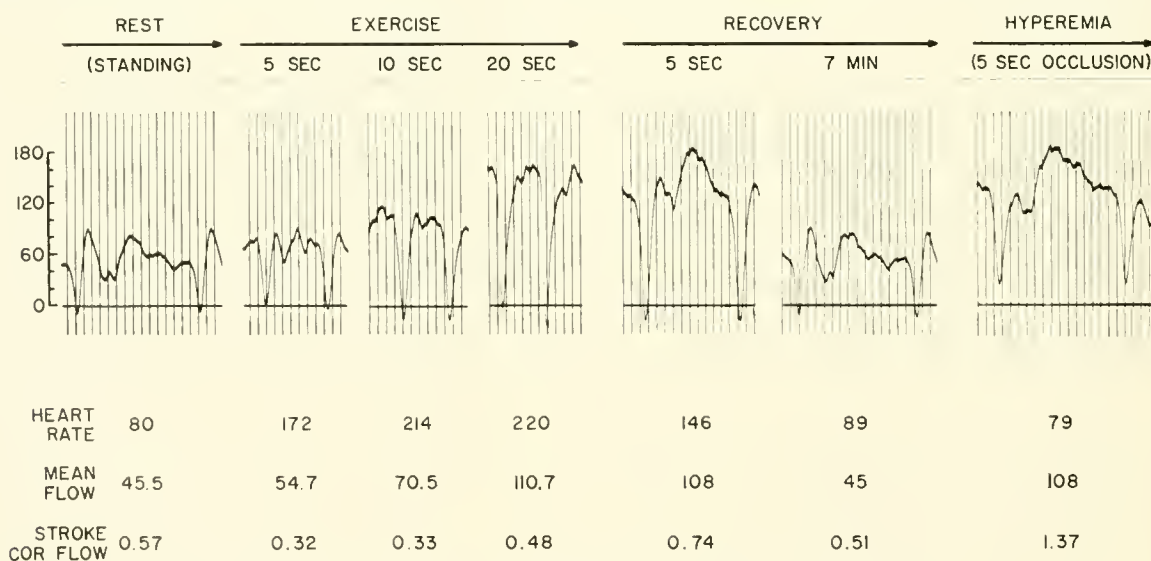


FIG. 11. Reproduction of sections of records taken from an exercising dog showing phasic coronary flow obtained by an electromagnetic flowmeter mounted on an internal mammary artery anastomosed to the left circumflex coronary artery. Anastomosis performed 17 months earlier and flow probe implanted 7 weeks before. Large greyhound at standing rest, running 3 min on treadmill at 10 mph, recovery, 5-sec occlusion of anastomosis to observe reactive hyperemia. [Khouri *et al.* (212).]

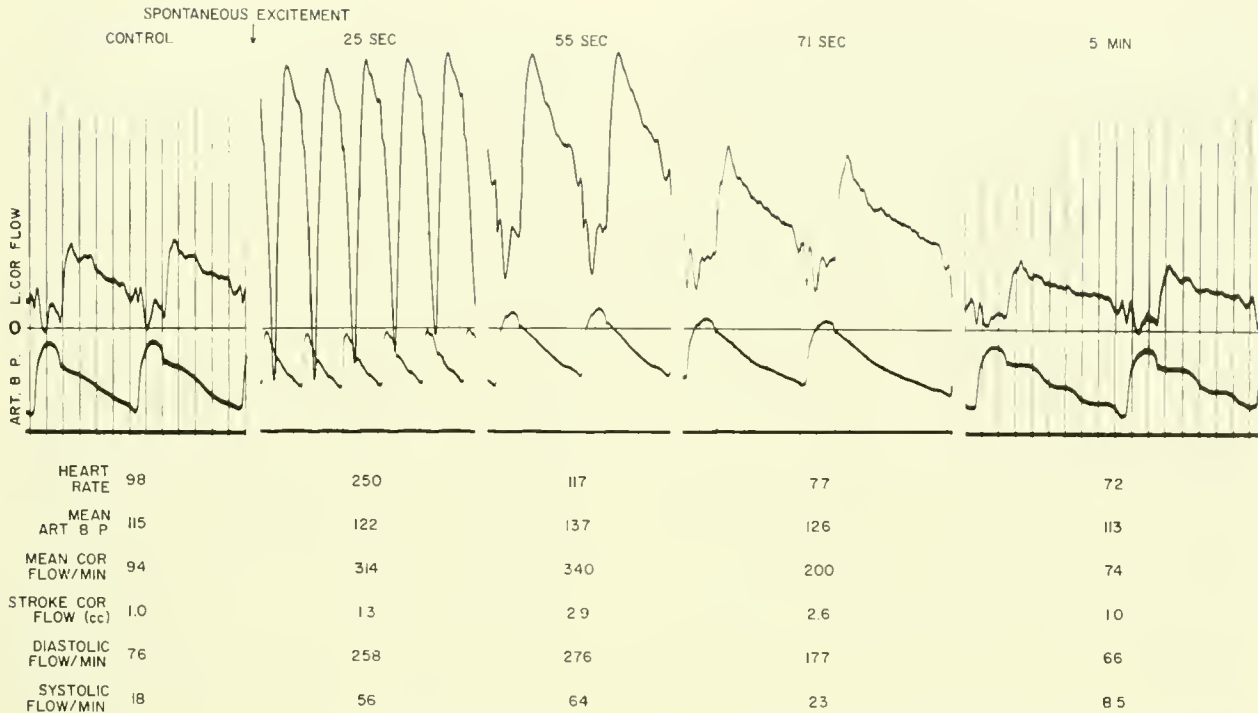


FIG. 12. Reproduction of sections from a continuous record in a conscious dog some days post-operative, showing effect of excitement on mean arterial blood pressure and stroke left circumflex flow, using strain gauge and electromagnetic flowmeter as in fig. 6. [Rayford *et al.* (301).]

experiments of a long-term chronic nature. It is not known, therefore, what application to the clinical situation can be made of present experiments.

AORTIC STENOSIS, PULMONARY HYPERTENSION, PULMONARY EMPHYSEMA AND COR PULMONALE. In the past, the coronary effects of stenosis of the aortic valves, cor pulmonale, pulmonary emphysema, and pulmonary hypertension associated with mountain sickness have not been studied in humans, largely for lack of an adequate method. Our information on these events thus comes largely from the dog.

In experiments with the isolated heart, elevation of right ventricular pressure by constriction of the pulmonary artery or elevation of left ventricular pressure by aortic constriction (coronary perfusion pressure kept constant) has been demonstrated to cause a reduction in blood flow to the myocardium of the right and left heart, respectively (153, 205). The flow decrease is attributed to the dominant effect of the direct mechanical inhibitive action of the increased vigor of the heart or the establishment of an unfavorable pressure gradient for right coronary drainage or both. In studies of the isolated supported dog heart, when coronary perfusion pressure (aortic) is kept constant, elevation of the resistance to right

ventricular output (an increase in cardiac work) does not affect total coronary outflow (313). This means that either the heart is performing the work much more economically or there is a large safety factor in the oxygen to be extracted. The latter is, of course, true in the isolated heart in which the extraction may be only 20 per cent, but in the normal heart no such wide margin of safety is available, extraction being of the order of 75 per cent. Therefore, it remains to be seen whether this dissociation of cardiac work and coronary flow in the isolated heart applies to a normal situation.

Acute elevation of right ventricular pressure by pulmonary artery constriction in the open-chest dog with constant heart rate is followed by a maintained increase up to 4 hours in systolic as well as diastolic blood flow in the right coronary artery in the presence of the same or some lowering of the aortic or central coronary artery pressure. In addition, venous outflow in the anterior cardiac veins increases greatly (153). During the sustained response, both right ventricular work and metabolism increase, the former being a result of the increased pulmonary arterial pressure and a small decrease in cardiac output, the latter elevation resulting from a combination of an increase in right coronary flow and a greater oxygen extrac-

tion from the right coronary blood. A high degree of coronary dilatation has obviously occurred since right coronary artery flow has increased throughout the cardiac cycle (especially in systole), in the presence of the same or a lower central coronary arterial pressure (153). The mechanisms responsible cannot be identified with certainty. They could be the opening of closed or partially closed capillaries and arterioles, the increased passage of blood through arteriovenous shunts, or increased metabolism. It is probably not explainable on the basis of myocardial hypoxia, since, if the right coronary flow is increased 300 to 400 per cent by a constant but very high infusion pressure, the flow increases still further when right ventricular pressure is elevated. Regardless, however, of the mechanism of coronary flow increase, elevation of right ventricular pressure can also be shown to have a flow-reducing effect antagonistic to the flow-promoting mechanisms. In the presence of an adequately maintained central coronary pressure, the sustained flow increase and decrease are preceded and followed by transient periods of flow reduction and elevation. The initial temporary decrease in flow is attributed to the dominant influence of augmented extravascular mechanical compression on the coronary vessels. The subsequent appearance of a sustained increased flow observed shortly thereafter indicates that the effect of coronary dilatation has exceeded the flow reducing effect of increased extravascular compression. The immediate and transient flow increase following abrupt lowering of intraventricular pressure is a rough index of the extent to which flow had previously been retarded by augmentation of extravascular compression.

Concurrent with the elevation of right coronary flow, left coronary flow and its drainage into the coronary sinus are significantly elevated (153, 196). The increase might be of significant magnitude to be determined in human subjects in the presence of an elevated right ventricular pressure, although this has not been found (312). It might be conjectured that the source of a portion of this increased left coronary blood is increased flow through the ventricular septum, much of which normally drains into the right ventricular cavity but which, because of high right ventricular pressure, might be diverted into the coronary sinus (265).

Such responses of flow and metabolism in the right myocardium to elevation of its cavity pressure are not peculiar to it. Elevation of left ventricular pressure by an aortic constriction central to the coronary ostia, i.e., between the aortic valves and coronary ostia to stimulate aortic stenosis, gives

trends for coronary flow and myocardial metabolism of the left ventricle identical to those found in the right ventricle (153).

These maintained changes in the coronary circulation could well be the early response in the human being to gradual moderate stenosis of the corresponding valves.

AORTIC INSUFFICIENCY. In patients with aortic insufficiency and lacking disease of the coronary ostia or arteries, the presence of chest pain resembling that due to myocardial ischemia is generally assigned to a reduction in coronary blood flow, this arising presumably from a reduction of the mean aortic or central coronary diastolic pressure. In the open-chest dog reversible aortic regurgitant flow has been accurately produced without valve injury, metered and controllably varied, while at the same time metering cardiac output. Aortic regurgitant flows in excess of the dog's resting cardiac output resulted in a marked decrease of effective cardiac output, a rise of peripheral resistance and left ventricular end-diastolic pressure, and a marked depression of the left ventricular pressure curve without significant change in mean left atrial pressure. No coronary flows were measured (390). In early experiments in the open-chest dog in rather poor condition (144, 153) reversible aortic insufficiency (umbrella-type aortic valve expanders) sufficient to lower aortic diastolic pressure decreases mean left coronary flow as a resultant of an increased systolic flow and a markedly reduced diastolic flow. On the other hand, Foltz *et al.* (119), from measurements on anesthetized dogs two or three days after the aortic cusps had been torn, found a considerable increase in coronary flow and myocardial oxygen usage. This latter finding has been confirmed by Wégria in acute experiments, and West in chronic dogs (386, 394). In patients with reduced diastolic pressure, wide pulse pressure and varying degrees of left ventricular enlargement, those without angina or failure have normal coronary hemodynamics; those with angina have a reduced coronary flow and cardiac oxygen usage; and those in failure have an increased coronary flow and oxygen usage (constant coronary A-V oxygen difference) (303). Such observations are difficult to interpret because of their small number, the lack of adequate control data, and the possibility of complicating disease of coronary ostia or arteries, or both.

MITRAL STENOSIS. The general hemodynamic effects from mitral stenosis include increased wedge pressure, pulmonary arterial pressure, right ventricular work,

and decreased systemic blood pressure, cardiac index, and cardiac work index. In small groups of human subjects, a normal or decreased coronary blood flow has been reported (216). In a large group of females, the above systemic changes have been found to be associated with a decrease in left ventricular coronary blood flow, increased coronary oxygen extraction, and decreased left ventricular oxygen utilization per unit of myocardium, as compared with normal females but not as compared with normal males (321). This depression of the left coronary circulation in the presence of a lowered activity of the left ventricle would be expected. Acceptance of these data, although in line with those previously reported in the intact dog (118), should possibly be deferred until previous work indicating that the left coronary circulation in the female is maintained at a considerably higher level than in the male (320) is confirmed.

MITRAL INSUFFICIENCY. Mitral regurgitation has been experimentally produced in the open-chest dog by permitting blood to flow externally from the left ventricular apex through a flowmeter into the left atrium during systole. Such controlled regurgitant flows, up to three times the resting cardiac output, are tolerated with only slight or mild alterations of effective cardiac output, aortic, left atrial and left ventricular pressures, total peripheral resistance, and the effective left ventricular function curves (45). In anesthetized open-chest dogs, acute mitral insufficiency of variable severity, produced by means of an umbrella-type valve spreader so as to allow a partial or incomplete return of the aortic flow to its control level, results in a moderate increase in coronary blood flow and myocardial oxygen usage and a reduced efficiency. Presumably, the left ventricle expends a significant amount of energy in regurgitating blood into the left atrium during mitral insufficiency (388). No comparable studies of this nature are available in humans.

AORTIC COARCTATION. With simulation of clinical coarctation by acute mechanical constriction of the thoracic aorta just beyond the left subclavian artery, venous return to the heart by way of the inferior vena cava is decreased but compensatory flow through various branches of the aortic arch may increase, with a resultant maintained cardiac output and elevated left ventricular work load. With greater aortic constriction, the net cardiac output decreases, causing the cardiac work to decrease. In either case, the coronary dilatation and increased flow arise in

large part from active changes in the bore of the coronary bed related to the metabolic demands, and, in part, passively from the increased blood pressure and moderately decreased heart rate (90, 207). The cardiac oxygen consumption is increased much more by this augmentation of pressure work than with an equal increase of volume work following transfusion (335). No chronic studies of aortic coarctation have been made because, owing to development of collateral circuits, the aorta may be first partially and then completely constricted at the arch without permanent development of hypertension proximal to the occlusion. In human coarctation not much change is reported in coronary flow and oxygen uptake, but this might be expected because systemic pressure is only mildly elevated (31). However, if true, the deviation might be explained by the fact that in these hearts, which are hypertrophied, there are fewer capillaries per unit of muscle to carry the oxygen and flow.

Hypertensive Cardiovascular Disease

An exception to the general picture of coronary compensation to increased systemic stress appears to be the response of the chronically hypertensive heart. In essential hypertension, with a normal cardiac output and elevated systemic blood pressure, the coronary flow and oxygen consumption per 100 g myocardium are unaltered while coronary resistance increases. This increased resistance is shared with the renal and cerebral circulations. Since these hearts are generally hypertrophied, total coronary flow and oxygen usage are probably increased. This deviation is explainable if it is assumed that such hearts with known coronary artery disease have an increased amount of perfused fibrotic tissue (31, 316).

Heart Failure

Although the underlying mechanisms for various types of heart failure may be different, the basic hemodynamic manifestations of cardiac failure are similar from causes such as congestive heart failure, anemia, anoxia, hemorrhagic shock, myocardial infarction, hyperthyroidism, and beriberi. Experimentally, such hearts exhibit depressed Starling or ventricular function curves (increased ratio of end-diastolic ventricular volume or ventricular filling pressure to stroke work), and show the characteristic optimum beyond which further stretching reduces the force of contraction and leads to myocardial failure. In acute heart failure in the open-chest dog,

with progressive deterioration of the right myocardium from pulmonary artery stenosis, the changes in coronary flow and oxygen usage per minute and per beat may be in the same direction (increase) as those described for the nonfailing right myocardium, but of lesser magnitude (see section on Valvular Disease). If the heart failure is severe enough, extravascular compression can become dominant over any active coronary dilatation from metabolic processes, and coronary flow and oxygen usage may be normal or decrease, with the oxygen extraction at times reaching 90 per cent (153). The coronary circulation in the heart, failing with severe aortic stenosis, undergoes similar changes (Gregg, unpublished data). When acute heart failure and chronic congestive failure simulating the human condition are induced by surgical complete heart block, changes in left coronary flow and ventricular oxygen consumption also rather closely parallel alterations in the reduced left ventricular work (355). In each instance, the mechanical efficiency of the myocardium drops, the total energy of liberation (oxygen consumption) being fairly well maintained, but the work falls off. The isolated mammalian heart or heart-lung is also characterized by deterioration of mechanical efficiency and on the same basis (74, 243). In chronic left heart failure due to rheumatic, arteriosclerotic, and hypertensive heart disease, the coronary circulation apparently responds by a slight increase in oxygen usage through maintenance of the left coronary flow and an increased coronary A-V oxygen difference. This corresponds with the changes indicated for the right heart in an early stage of failure. As is true for the heart-lung or isolated heart, such hearts have considerable difficulty in transforming released energy into realizable work. Studies of the coronary circulation in high-output failure from excessive transfusion or a chronic aorta-caval fistula are not available. In the anesthetized open-chest dog, however, an acute arteriovenous fistula sufficient to increase cardiac output and cardiac work causes considerable augmentation of stroke coronary flow and stroke coronary oxygen even in the presence of a sizeable decrease in arterial blood pressure (389).

When acute heart failure induced by pulmonary artery constriction has advanced to the stage where systemic blood pressure is low, left ventricular size is small, right ventricular size is large, and release of the constriction does not restore ventricular working capacity, then the use of arterial transfusion with a pump temporarily promotes functional recovery of the heart (increase in arterial and coronary perfusion

pressure, coronary flow, cardiac output, cardiac work, and myocardial vigor, decrease in cardiac size and coronary A-V oxygen difference). Veno-arterial pumping accentuates and makes more permanent these beneficial changes. Since an increase in coronary flow invariably precedes recovery of the heart, it suggests that it is a primary stimulus through an effect on myocardial metabolism for increased ventricular performance and decrease in heart size (14).

Postmortem specimens from human patients may show myocardial edema (increased water, Na and Cl content per unit of myocardium) in the presence of congestive heart failure, acute infarction, and ischemic areas. Very often, however, previous drug administration, together with agonal and postmortem changes, makes interpretation difficult. The isolated dog heart does not develop edema when directly perfused from a donor dog, but increased myocardial water content is found after acute cardiac injury (over-distended ventricle), excessive perfusion pressure, increased coronary venous pressure, and by perfusion with blood from a disposable bag oxygenator system. It occurs spontaneously in the failing heart-lung preparation and in chronic heart failure produced experimentally by thoracocaval constriction, pulmonary stenosis, and tricuspid insufficiency, separately or together. The mechanism or mechanisms involved are unknown, but in these chronic preparations, elevation of right atrial pressure seems to be a major pathogenic factor in its formation. Whether its presence contributes to abnormal cardiac function or whether its prevention or reversal is a therapeutic objective in the management of heart disease is a moot question (329, 409).

Hemorrhagic Shock

Standardized oligemic shock in dogs is characterized during the hypotensive phase by a decrease in cardiac output, systemic blood pressure, cardiac work, stroke volume and stroke work, and by an increase in heart rate and an adequate central venous pressure. Coronary flow and coronary resistance are greatly decreased but the coronary flow fraction of cardiac output is increased (102). Coronary flow is generally greater and the resistance generally less than can be accounted for by a simple decline in arterial blood pressure (281). At the same time, the oxygen uptake decreases and the coronary arteriovenous oxygen difference is generally unchanged (166). The coronary response to sustained hypotension through

spinal anesthesia or injection of procaine and Etamon is similar (168). With partial or complete restoration to normal systemic blood pressure by reinfusion (intra-arterial and intravenous routes are equally effective) (56, 361), coronary flow is greater and flow resistance is less than at an equivalent arterial blood pressure in the preshock state.

The fact that early in the hypotensive phase neither ventricular end-diastolic pressure nor atrial pressure rises indicates that the functional capacity of the heart is adequate for the work performed. However, that myocardial depression or failure is partially responsible for the hemorrhagic shock syndrome is suggested by different observations. *a)* After prolonged hypotension, there may be evident cardiac dilatation and elevated left and right atrial pressures with the heart eventually proceeding to ventricular fibrillation or standstill (331). With spontaneous cardiovascular decay after reinfusion, the atrial pressure may be at a normal or elevated level despite large cardiac output reduction (402). *b)* During prolonged oligemic hypotension, as the animal starts to take up blood from the reservoir to maintain its falling blood pressure, the atrial pressure may rise to very high levels (163). Gross and microscopic evidence of myocardial injury appears in both reversible and irreversible shock. Such myocardial depression could be caused by an insufficient coronary flow during either the hypotensive or the post-hemorrhagic periods. The high coronary flow during the restoration period would seem to preclude an inadequate coronary flow as an adequate explanation. During the hypotensive period, the actual coronary flow is greatly curtailed. The problem is whether the associated sizeable reduction in coronary resistance is sufficient to permit enough blood to reach the myocardium to prevent it from failing. In some instances, at least, this loss of myocardial contractility is consequent upon an insufficient coronary flow, since the relation of atrial pressure to cardiac size can be reversed by increasing left coronary flow mildly with a pump, without change in either the hypotension or blood volume (331).

The work just discussed has been largely restricted to studies in experimental animals exposed to anesthesia, surgery, and varying amounts of traumatic insult. More proper studies might be conducted in intact conscious dogs; this is possible with methodology now available. This type of study has been made with the use of modified and improved electromagnetic flowmeters which were chronically implanted on the left coronary artery as well as the aorta and various

systemic arteries (159). The experiments confirm previous findings that, of all the arterial beds, only the coronary shows a decreased vascular resistance during hemorrhagic irreversible shock, and add new information regarding the compensatory behavior of the left coronary vascular bed. The coronary pressure-flow ratio moderately increases during hemorrhage, progressively decreases during the hypotensive period as the coronary flow increases spontaneously, and is temporarily restored during the reinfusion. During the irreversible period, in which the coronary flow is fairly well maintained, the pressure-flow ratio again drops. The resistance, however, to coronary flow is somewhat less during the period of spontaneous decay than during the initial hypotensive period. These pressure-flow changes may have their explanation in certain characteristic changes in the coronary flow pattern. The phasic flow pattern, initially some distance above the zero flow line throughout the cardiac cycle, moves closer to the zero flow line during hemorrhage, and backflow may appear during systole. The magnitude of the flow pattern, however, increases, indicating increased vigor of contraction. As the hypotensive period progresses, flow is re-established in systole and increased somewhat in diastole. Following reinfusion, and late in the period of spontaneous hemodynamic decay, the flow pattern may resemble somewhat the prevailing aortic pressure pulse with the systolic flow equal to or exceeding the diastolic flow. The mechanisms whereby coronary systolic flow is thus preferentially enhanced are not known.

Hypothermia

The circulatory and metabolic adjustments of the heart during hypothermia have been partially explored (87). When the body temperature is dropped from 37°C to 20–28°C, by immersion hypothermia or by cooling the systemic arterial blood flow, the associated changes that occur which tend to reduce the coronary flow are a diminution in blood and muscle temperatures, cardiac output, heart rate, cardiac work, and oxygen usage by the heart, an increased blood viscosity and a greatly lengthened period of ventricular systole. The coronary A-V oxygen difference remains about normal or decreases (103, 128, 175, 180, 322). Opposing these factors are the relaxation of the major coronary vessels, which is known to occur with hypothermia, and dilatation of the coronary bed caused by the hypotension *per se* (25, 177). As a resultant of these determinants,

coronary flow is decreased at low temperature. However, the per cent reduction in cardiac output is greater than that in coronary flow, which results in an increase in the coronary fraction of cardiac output at temperatures of 25 to 26 C (103, 322). There is little change, a decrease, or an increase in peripheral resistance in the coronary bed, whereas in the systemic bed an increase in peripheral resistance invariably occurs (177, 322). A constant or increasing mechanical efficiency is usually observed in the open- or closed-chest dog (128, 175) although it has been reported to fall (103, 198). Similarly, in the heart-lung preparation or isolated heart, the mechanical efficiency is fairly constant when cardiac work per beat (same stroke volume and arterial blood pressure) and heart rate are constant (15). Myocardial function appears to be adequate and myocardial hypoxia not to exist (198). However, many hearts are apparently not too far from failure because if total venous inflow occlusion (which decreases coronary flow close to zero) is now added to permit open cardiomy, myocardial failure supervenes, as evidenced by elevation in mean right atrial pressure and post-mortem findings. This trend can be reversed by perfusion of the coronary system with small volumes of oxygenated blood (239).

Hyperthermia

The systemic dynamic changes resulting from elevation of body temperature by fever or external application of heat (hot baths, diathermy) are quite similar in man and dog, are well documented, and include considerable elevation of heart rate, blood pressure, cardiac output, right and left ventricular work, a decreased peripheral resistance and a constant stroke volume and stroke work. The little information available on the associated coronary changes indicates that a large elevation of body temperature (up to 105 F) by means of diathermy, in the closed-chest dog, increases considerably coronary blood flow, myocardial oxygen usage, coronary A-V oxygen difference, increases mildly the stroke coronary oxygen usage, decreases external efficiency, and leaves unchanged the stroke coronary flow and coronary resistance (257). In open-chest dogs with an initial hypotensive systemic blood pressure, diathermy has no effect on coronary flow (253). In the heart-lung preparation, when the myocardium is warmed, coronary flow and oxygen usage are increased; but they are not when the coronary blood is warmed (10).

Summary

Over the years, the basic mechanisms affecting coronary flow and oxygen usage have been related experimentally to various parameters, and the statement is often made that there is one controlling or unifying influence for coronary flow per heart beat and also one for oxygen usage of the left myocardium per cardiac cycle. *a)* Directional changes in stroke coronary flow correlate with stroke coronary oxygen usage. This is so, however, because normally most oxygen is removed from the coronary blood and the level of coronary sinus oxygen is usually fairly constant under stress, i.e., it does not change more than 10 to 15 per cent. In those instances in which the coronary arteriovenous oxygen difference increases or decreases by this amount, it does not greatly affect the relation of coronary flow to oxygen usage since the change is very small relative to the magnitude of the coronary flow change, but this does not document a functional correlation between these parameters. *b)* The stroke coronary flow and stroke coronary oxygen correlate fairly well with the stroke work under a variety of conditions of changing systemic stress, but it is possible to so regulate experiments that the response of the coronary circulation is dissociated from stroke work. *c)* The exceptions to the usual correlation of stroke work and coronary oxygen usage constitute a group of conditions in which the outflow channels of the two ventricles have been restricted in some manner. In these, one can show excellent correlation of the stroke coronary flow and oxygen usage with the mean systolic arterial blood pressure alone, or with the product of the systolic blood pressure and the duration of systole, the so-called "tension-time index." However, experiments in the unanesthetized dog during exercise and excitement do not always support this view. In addition, there is quite a list of determinants that have been thought to be fundamental. Attempts have been made to relate coronary flow and oxygen usage to the mean arterial blood pressure, ventricular filling pressure or mean atrial pressure, ventricular diastolic volume or fiber length, tension within the ventricular wall, oxygen tension of the arterial blood, oxygen tension within the myocardium, action of local metabolites or vasodilating substances. Possibly, the best correlation of all should be with the reduction of cytochrome oxidase and the needs of the hydrogen transport system. Probably no final answer is available. Final decision as to whether any of these determinants of coronary flow or oxygen usage are

primary or empirical must await the necessary measurements under normal conditions of stress without anesthesia or surgical insult.

DRUGS VERSUS THE CORONARY CIRCULATION

The pertinent literature has been reviewed (7, 13, 49, 68, 145, 153, 209, 238, 275, 384, 413). Consideration will be given here only to the effects of a few selected drugs on the coronary circulation in the normal state and in the presence of coronary artery disease.

Drugs may be effective in altering the normal and collateral myocardial blood supply by a direct effect on the vasomotor state of the vessels, by an increase or decrease in central blood pressure, by myocardial stimulation or depression, by a change in the cardiac workload through extracardiac phenomena, or by electrolyte, pH or gaseous alterations of the blood perfusing the coronary bed. It is interesting to know whether a drug affects the extravascular and intravascular resistances of the coronary bed, but it is more important to know its effect upon the supply of oxygen to the myocardium, the oxygen used by the myocardium, and the efficiency of the heart in the use of its oxygen for the work performed. In addition, a pharmacological agent may be able to improve the oxygen utilization for external work of the heart without an increase in coronary blood flow or oxygen extraction.

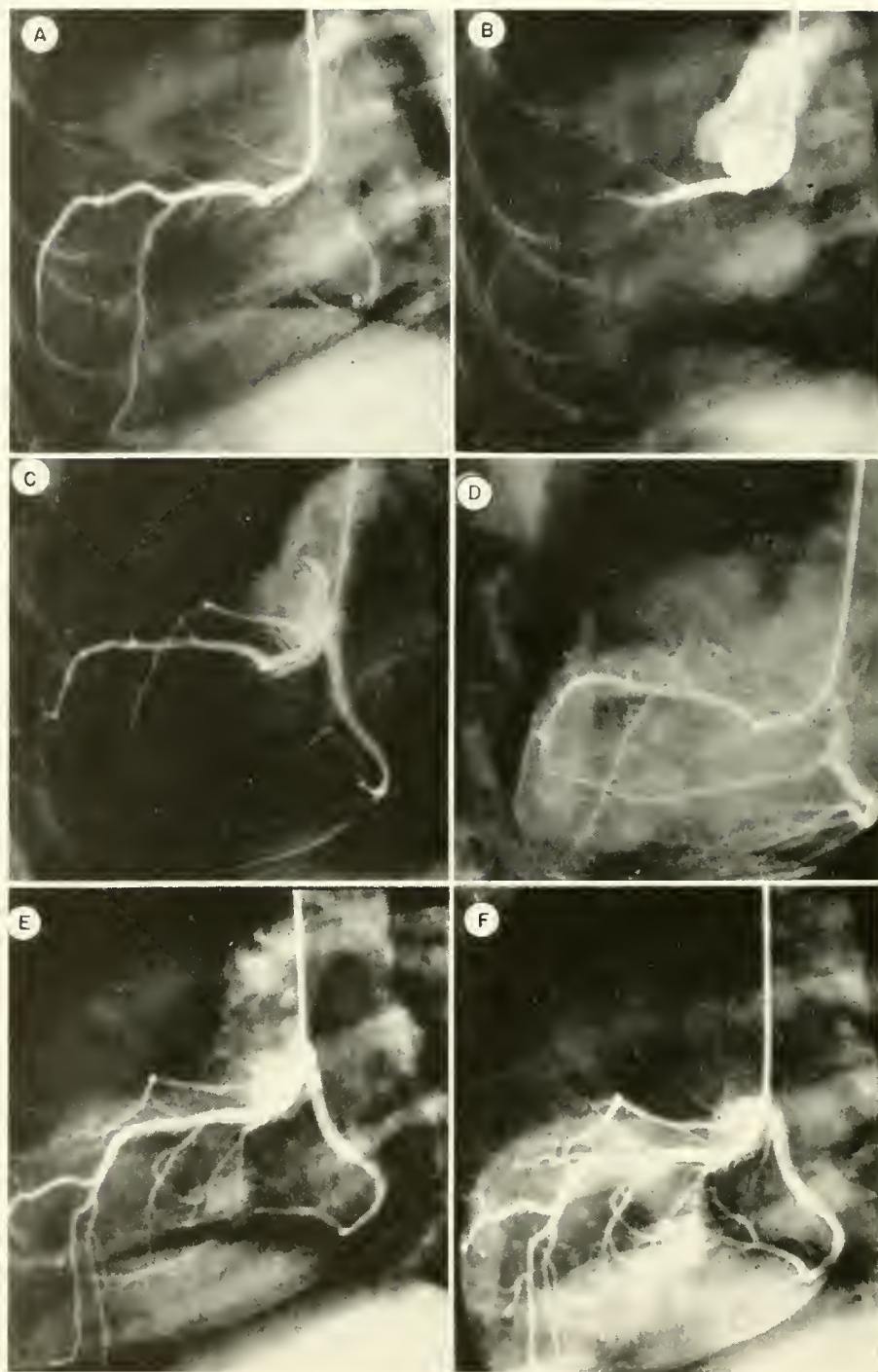
In order to properly evaluate an agent, the following information is necessary: *a*) coronary blood flow, *b*) arteriovenous oxygen difference across the coronary bed, *c*) blood pressure, *d*) cardiac output, *e*) myocardial contractility, and *f*) heart rate. From these data, the myocardial oxygen availability and usage, cardiac work and efficiency can be calculated.

Few drugs have been completely studied. The pharmacologic agents will be considered from the standpoint of: *a*) the effects of therapeutic or potentially therapeutic drugs on the normal myocardium undergoing normal or excessive stress, and *b*) the effects of nontherapeutic drugs on the normally stressed myocardium. In the normal and hypertensive heart, the ganglionic blockers such as hexamethonium decrease both cardiac work and myocardial oxygen availability but not the oxygen usage (73, 162). Nitroglycerin has no apparent direct effect on the amount of free energy released with each contraction of the myocardium either before or after partial coronary artery occlusion, but rather reduces

hemodynamic workload by a decrease in left atrial filling pressure (75). Experiments in dogs with sodium nitrite or nitroglycerin injected into the left coronary artery show that the coronary arteries and their small branches dilate (fig. 13) (393), and that the flow increases greatly in both systole and diastole and in the presence of a decreased central coronary pressure, cardiac output, cardiac work, a constant heart rate and only a slight decrease in the systolic:diastolic ratio. Hence, the conclusion is inescapable that these drugs exert a vasodilating action on the coronary vessels (41). This could arise from a direct effect of the drug on the coronary vessels since cardiac metabolism is not increased (decreased coronary A-V oxygen difference and increased coronary flow) (94, 333). Experiments in normal man with nitroglycerin, however, show an increased coronary blood flow with an increased myocardial oxygen uptake (constant coronary A-V oxygen difference and increased coronary flow), decreased cardiac work and decreased cardiac efficiency (42). Furthermore, in patients with coronary artery disease, this drug does not increase coronary flow while, with a steady oxygen extraction, it decreases cardiac work (decreased blood pressure and cardiac output) (138). These data raise the old question of the applicability of knowledge obtained in normal animal or human studies to the diseased states. If these studies should be confirmed in patients during anginal attacks, other theories for the action of nitroglycerin must be considered. One theory holds that nitroglycerin blocks the anoxia-inducing effect of the catecholamines on the heart (296), but an antiadrenergic action could not be demonstrated for this drug (94). One might postulate that a decrease in cardiac work secondary to the decrease in blood pressure, in the presence of a stable oxygen consumption, may be helpful to the myocardium despite a calculated decrease in myocardial efficiency. Present calculations include only evaluation of the external efficiency of the heart. If such hearts are using all the oxygen they could extract at a given workload, then a decrease in this work, at the same level of oxygen consumption, might be beneficial.

With the xanthines mean coronary flow is increased, this being the net result of a marked increase during diastole and a decrease during systole which occurs in the presence of a normal or mildly decreased blood pressure and without significant change in cycle length or systolic:diastolic ratio. Visually, the heart shows increased vigor and its metabolism and work are increased (41). Nikethamide acts similarly by

FIG. 13. Effects of coronary arterial injection of Pitressin, nitroglycerin, and acetylcholine in the anesthetized dog. Catheter in the first part of the anterior descendens branch (left lateral view). Radiopaque material injected in all cases 5 cc. *A*: control angiogram (BP 150/115; HR 90) before Pitressin. *B*: (BP 145/115; HR 85) 1 min after Pitressin injection (0.008 units/kg). *C*: control angiogram (BP 175/125; HR 75). *D*: (BP 165/115 HR 78) after nitroglycerin injection (5 μ g/kg). *E*: control (BP 177/115; HR 84). *F*: (BP 170/117; HR 84) immediately after acetylcholine injection (0.04 μ g/kg). [Modified after West & Guzman (393).]



increasing the oxygen available to the myocardium but at the expense of an increased oxygen usage and cardiac work (91). It would probably be preferable to increase the oxygen availability without stimulation of myocardial oxygen metabolism, as has been shown for nitroglycerin and papaverine in animal studies

(75, 117, 214). Hydralazine, which may precipitate anginal attacks in hypertensive patients, possesses what are usually considered the desired properties for a coronary vasodilator: it increases coronary blood flow, increases oxygen availability, and does not alter the oxygen uptake of the myocardium (316).

It would appear that our concepts of the "ideal" agent for coronary artery disease must be revised.

Information is confusing regarding the coronary effects of khellin, a drug used in the eastern Mediterranean regions since ancient times in renal colic and ureteral spasm. Interest in its possible cardiac effect arose as the result of the discovery that, orally or intravenously, it acts for many hours as an extremely potent coronary vasodilator in the heart-lung preparation and in the heart in situ. In the doses used, it has no effect on the general blood pressure and does not increase the oxygen requirements of the heart, i.e., it acts only to relax the intrinsic smooth muscle of the coronary arterioles (153). However, others (109) did not find it effective on the coronary or systemic circulation of the anesthetized dog.

There is little doubt that digitalis augments ventricular contractility and the peripheral circulation (48, 314). However, in normal human subjects, strophanthus apparently has a deleterious effect since it decreases cardiac work and efficiency without altering coronary flow, oxygen supply, or usage of the myocardium (31). Conversely, in the patient with congestive heart failure, it has a salutary effect by acting to increase cardiac work and efficiency without using more oxygen or altering the coronary circulation. This is another case in which the action of a drug is entirely different in the normal subject from what it is in the diseased subject.

Ever since Favarger (110), in 1887, claimed that excessive tobacco smoking produced coronary vasoconstriction which, repeated over many years, gradually resulted in organic heart disease, tobacco has been considered an important cause of coronary disease. The alterations of the ECG (T-wave depression and sagging of the S-T segment) and of the BCG in the normal heart, or the heart with coronary arterial disease, that follow inhalation of tobacco smoke or administration of nicotine, have been generally thought to result either from coronary arterial constriction or from an increase in the work of the heart beyond the capacity of the coronary arteries to supply the necessary metabolic requirements of the myocardium. Observations on the normal heart of the anesthetized dog do not support this view. Intracoronary nicotine injection greatly increases myocardial contractility, and in dogs pretreated with Dopa, nicotine increases considerably the myocardial catecholamine concentration (202). The circulatory responses to administration of cigarette smoke or nicotine generally include elevation of heart rate, blood pressure, cardiac output, cardiac

work, left coronary flow, myocardial oxygen usage, and a decrease in coronary vascular resistance. The coronary oxygen extraction may be decreased, and often the oxygen usage may be transiently unchanged or decreased (213). These responses can all be blocked by injection of tetraethylammonium chloride. These effects parallel those observed with epinephrine injection and are presumably related to its release. The response to nicotine of the coronary flow, in dogs with coronary insufficiency from coronary arterial ligation or gradual coronary artery narrowing, is considerably less than in dogs with normal coronary arteries (20); in the isolated atherosclerotic rabbit heart, it decreases coronary flow (364). In normal man, earlier findings indicate that cigarette smoking increases coronary blood flow and heart rate, and decreases coronary vascular resistance in the presence of reduced systemic dynamics, whereas in patients with coronary artery disease, smoking causes no appreciable change in coronary flow and myocardial oxygen consumption in the presence of increased heart rate, blood pressure, cardiac output, and cardiac work (304). This suggests that the electrocardiographic changes observed during smoking are the result of a relatively deficient oxygen supply to the myocardium in the presence of increased oxygen needs (increased cardiac work). Later reports from the same laboratory indicate, in subjects both normal and with coronary artery disease, that smoking increases heart rate, blood pressure, and left ventricular work but does not alter coronary flow or cardiac oxygen usage (306). Decision as to the action of smoking and nicotine in human subjects must be deferred until the various neurohumoral responses evoked are better understood and better methodology is available.

Certain agents which increase coronary blood flow will not be discussed because of the scant information available. Isoproterenol, histamine, antihistamines, heparin, Dicumarol, ethanol, 5-hydroxytryptamine, Amplivix, and RA-8 increase coronary flow in animal preparations (62, 200, 224, 238, 299, 384). Reports are conflicting regarding Metrazol, quinidine, quinine, and morphine (299, 318, 384). Only two drugs, Pitressin and angiotensin, decrease coronary blood flow without a decrease in central blood pressure (150).

For clinical use in angina pectoris, drugs are evaluated in patients by methods involving their ability to alter the electrocardiographic response to an exercise test or by drug-placebo (double blind) studies (70, 157). The selection of patients for these

trials is very difficult due to the variability of the disease and its response to many extraneous factors. Nitroglycerin remains the only universally preferred treatment. Other agents, including the long-acting nitrates, have received some favorable but also many unfavorable reports. The mode of action of the monoamine oxidases is unknown although the clinically beneficial but toxic iproniazid has been demonstrated to increase coronary flow and depress cardiac contraction in isolated hearts (160). Anticholesterol agents and thyroid are used in the hope of decreasing the atherosclerotic process, but long-term studies are needed to assess their value. However, study of hyperthyroid patients shows that their myocardial oxygen utilization is increased more than would be expected from the increased heart rate (317).

Table 1 is a compilation of data concerning the action of the vasopressor agents most commonly used in cardiogenic shock. Since most of these studies were performed in normal animals or man, the question again arises whether the information can be applied to the diseased state. Against such application is the demonstration that drugs may act differently in a normal, as compared to a failing heart, i.e., mephentermine may exert a myocardial oxygen-conserving

effect in failing animal hearts but an oxygen-wasting action in normal hearts (391). Since the etiology of cardiogenic shock is undetermined (decreased peripheral resistance, or myocardial failure or both), controversy exists regarding its treatment. The question concerns whether an agent should be used which not only increases coronary flow and blood pressure (methoxamine), but also stimulates the myocardium and, therefore, increases myocardial oxygen consumption (epinephrine, levarterenol, metaraminol, and mephentermine) (13, 237). It appears that clinical results favor the latter concept, for levarterenol has met with the most success. Also, in animal studies the vasopressor agents which stimulate myocardial contractility and lower atrial pressure are more beneficial to the "failing" heart (332). However, methoxamine has been shown to be of use for increasing the blood pressure and coronary flow in hemorrhagic shock in animals, and also in cardiogenic shock in patients (13). A useful agent for cardiogenic shock should increase coronary flow, stimulate myocardial contractility, and raise the blood pressure and cardiac output, but should not increase myocardial oxygen consumption in relation to its workload. It was pointed out above that myo-

TABLE 1. *Pressor Agents Used in Cardiogenic Shock**

| Drug | Route | Blood Pressure Systolic Diastolic | Heart Rate | Myo- cardial Force of Contraction | Coro- nary Blood Flow | Myo- cardial O ₂ Uptake | Coro- nary A-V O ₂ Difference | Cardiac Output | Cardiac Work | Cardiac Effi- ciency | Total Periph- eral Re- sistance | Right Atrial Pres- sure |
|----------------------------------|-------|-----------------------------------------|------------|--------------------------------------------|--------------------------------|---------------------------------------------|---------------------------------------------------|-------------------|-----------------|----------------------------|------------------------------------------|----------------------------------|
| Epinephrine (Adrenaline) | I. V. | +/- | +(±) | (+) | (+) | (+) | (-) | + | + | (-) | - | |
| | I. C. | | | (+) | (+) | (+) | (+) | | | | | |
| Levarterenol (Levophed) | I. V. | +/+ | -(±) | (+) | (+) | (+) | (-) | -(±) | +(+) | (-) | + | (-) |
| | I. C. | | | (+) | (+) | (+) | (+) | | | | | |
| Ephedrine | I. V. | +/o | + | (±) | (+) | | | +(±) | + | | - | |
| | I. C. | | | | | | | | | | | |
| Metaraminol (Aramine) | I. V. | +/+ | - | (+) | (+) | | | o(±) | + | | + | (-) |
| | I. C. | | | (+) | (+) | | | | | | | |
| Mephentermine (Wyamine) | I. V. | +/+ | - | (+) | (+) | (+) | (-) | o(±) | + | (-) | +(o) | (-) |
| | I. C. | | | (+) | (+) | | | | | | | |
| Phenylephrine (Neosynephrine) | I. V. | +/+ | - | (+) | (+) | | | ± | + | | + | +† |
| | I. C. | | | (+) | (+) | | | | | | | |
| Methoxamine (Vasoxyl) | I. V. | +/+ | - | (o) | (+) | | | (-) | (-) | | (+) | (+) |
| | I. C. | | | (o) | (o) | | | | | | | |

* Results in man. Figures in parentheses indicate if dogs react differently or if only dog results are available.

Key: I. V. = intravenous; I. C. = intracoronary; + = increase; o = no change; - = decrease; ± = variable effects or conflicting data; † = venous pressure.

cardiac contractility and oxygen consumption may be dissociated. Such drugs may be available but more experimental proof is necessary.

CORONARY ARTERY DISEASE

The basic pathological lesion in coronary artery disease is the atheroma which eventually leads to narrowing or occlusion of the coronary artery lumen by progressive intimal thickening, intimal ulceration, hemorrhage or superimposed thrombosis. Thrombosis on an arteriosclerotic basis (43%), arteriosclerosis with and without infarction (41%), and intramural hemorrhage (8%), also presumably on an arteriosclerotic basis, account for about 90 per cent of coronary artery lesions (379). Coronary artery narrowing or occlusions are limited to the three main coronary arteries (50%) and their primary branches (50%), and are almost entirely epicardial (100). The lesions are localized, segmental, and multiple (avg. 2.5/heart), and 70 per cent occur within 3 to 4 cm of the coronary ostia (39, 184). As a result of this occlusive process, the myocardial circulation is reduced to a variable degree, depending upon the nature and extent of the lesion and the extent to which intercoronary artery collateral development takes place. Serious consequences occur when the extent of the former is large or the latter mechanism fails to compensate for the ischemic changes produced by the atherosclerotic process. The following, singly or together, may then take place: angina pectoris, myocardial infarction, mechanical failure, or sudden death.

Since Heberden's classic description in 1768 of the syndrome of angina pectoris, much effort by medical investigators has been directed toward this problem. While there are some dissenting voices (297), general consideration indicates that the production of pain arises from stimulation of sensory cardiac nerve endings which, in turn, arises from imbalance in the heart between supply and demand of oxygen. Sensory nerve endings of the heart (and aorta) are present in the myocardium, endocardium, and epicardium, and in the adventitia of the coronary arteries. Their associated neurones converge in the periarterial plexus of the coronary arteries, continue through the superficial and deep cardiac plexuses and course in the middle and inferior cardiac nerves to join the corresponding cervical ganglia of the sympathetic chain. These centrally bound fibers then descend to the upper thoracic ganglia and reach their cells in the

spinal ganglia by passing through the white rami communicantes into the first thoracic and upper 4 or 5 intercostal nerves. They cross to the opposite spinothalamic tract and course through the brain stem to the thalamus (397, 401).

From the preceding, it is obvious that pain could be relieved in different ways: by raising the cerebral level or threshold for pain perception, by attenuation of factors in the environment that lead to stimulation of the cardiac pain end organs, by the induction of proper coronary vasodilatation. However, the physiological evaluation of angina pectoris, and of the effects of medical and surgical therapy on it, is limited to study of the relief of the angina of effort in cases where attempts are made to delete the subjective element of pain, and to the measurement in equivocal cases of the coronary flow response to vasodilator drugs such as nitroglycerin to determine the ability of the coronary bed to dilate on demand. The latter is predicated upon the experimental finding in advanced coronary artery disease of fixation of the coronary flow when challenged by nitroglycerin (44). Whether the ability of a drug to diminish anginal episodes or to improve the electrocardiographic response in exercise is an objective measure of positive benefit to a stressed myocardium is still debatable. This is so because it is not known to what extent the influence of the physiology of sensation on angina has been removed, and the assumption must necessarily be made that the electrocardiographic response correctly indicates myocardial hypoxia or ischemia.

As yet, experimental studies directly attacking the problem of coronary atherosclerosis have not been productive in elucidating the mechanism of or prevention of the lesion. However, the functional consequences and compensatory physiological responses to controlled experimental coronary constriction and occlusion, or to the loss of functional myocardial areas in acute and chronic animals, have been extensively investigated.

No standardizable preparation with coronary artery constriction or occlusion similar to that of the human has been worked out for the experimental animal. Naturally occurring or experimentally induced coronary lesions (dog and rabbit) are similar in many respects to the human lesions, but the endothelium remains intact and ulceration and thrombus formation do not occur. For acute or chronic experiments, an artery may be tied off abruptly and completely or partially, by inserting a probe between the artery and suture (98), or acute

(and at times chronic) preparations can be made by the intracoronary artery injection of lycopodium spores (392) or plastic microspheres (2, 34). More gradual constriction of the lumen, however, may reduce the incidence of ventricular fibrillation, minimize infarction, and augment collateral development. The introduction of intracoronary clots, the induction of coronary thrombosis by electrical means (194, 327), the application to the artery of adjustable Goldblatt clamps, irritant rings or bands of cellophane or bakelite, osmotic clamps, or swelling casein rings, can all ultimately lead to complete coronary artery occlusion (123, 362, 375). Unfortunately, by none of these methods can the time of complete occlusion be known in vivo, nor could the per cent reduction in flow be predicted even if the extent of local reduction in vessel lumen were known. As in other vessels, the effectiveness of a given localized constriction in reducing flow may be large or small and will vary in inverse relation to the peripheral resistance of the vascular bed and lumen of the constricted segment, and in direct relation to the flow velocity, blood viscosity, and axial length of the constricted area (153).

The hearts of persons afflicted with the clinical signs and symptoms of coronary artery disease, or of animals in which coronary insufficiency has been experimentally induced, generally present a dual problem. The area of the heart with a normally functioning coronary arterial system carries much, if not most, of the burden of metabolism and work of the poorly nourished myocardium, in addition to its own. If the handicapped area of myocardium is large, then the normal portion of the myocardium is heavily loaded and stressed in its efforts to carry the total performance of the heart. In the remaining area of the myocardium, i.e., that handicapped by sclerosed vessels, or vessels not carrying a normal supply of oxygen to the myocardium, the supply of blood and oxygen is too small.

Natural Responses of the Normal but Overstressed Portion of the Myocardium

If the ligation or constriction of a coronary artery is severe enough, useful function is lost within 1 min in the myocardium fed by it, since the muscle mass which was shortening during systole now bulges and lengthens (359). The fact that the area lengthens rather than shortens during systole does not mean that the area is not viable, but rather that although attempting to shorten, the force it exerts is so weak as

to be overbalanced by the intraventricular pressure which distends it. Since, as will be discussed later, the collateral flow does not increase for some hours, any early natural cardiac compensation must occur, not by improvement of the circulation in the affected area, but through enhanced action of the normal myocardium which is not involved. Loss of contracting blocks of muscle following coronary artery occlusion not only reduces the total myocardial force available for raising intraventricular tension, but some of this pressure is spent in stretching the ischemia area and thus is lost for expelling blood into the aorta. The immediate consequences of this, producing a hypodynamic ventricle, are a reduction in left ventricular systolic pressure, aortic pulse pressure, systolic and diastolic pressures, duration of systole, and, especially, stroke volume and stroke work. In this situation, left coronary inflow decreases considerably (120, 385). However, within a few minutes, the normal portion of the heart may put into operation compensatory mechanisms by means of which dynamic conditions are largely restored to normal, provided the normal myocardium is in a good responsive condition. In this situation of increased cardiac work per unit of functioning myocardium, coronary flow, arteriovenous oxygen difference, and metabolism of the left ventricle increase. The increase in oxygen uptake is equal to, and at times can be much more than, that lost by the deletion of non-contractile muscle.

However, not all hearts react as well because the viable portion of the myocardium may not initially respond to stretch, or the same lack of response may occur later after an initial salutary response. This has been especially studied in dog hearts in which interference with the coronary circulation has been by coronary ligation, or by intracoronary injection of plastic microspheres (2, 33). This leads to acute or progressive heart failure associated with profound hypotension, decreased cardiac output and stroke volume, and the clinical signs and symptoms of a shock-like state similar to that which occurs following the loss of blood or plasma. The clinical inference that this is due to supervention of local coronary spasm or peripheral circulatory failure has not received experimental support. Most evidence indicates that no primary insufficiency of the resistance or capacity vessels exists, nor even any noxious reflex to which the cause of shock could be attributed, nor does such shock arise, apparently, from reflex coronary constriction in the nonoccluded coronary artery (57, 153, 233, 254). The experiments of Kuhn *et al.* (219)

could, however, be interpreted differently. There are many reasons to favor the view that in this situation, circulatory failure not due to severe irregularity of the heart beat is due successively to: *a*) defection of useful contractions in the ischemic area, *b*) a loss of contractile energy through expansion of the affected area and *d*) failure of the still viable fractions to compensate adequately.

Since protracted hypotension can, at times, lead to myocardial damage and failure, and since experimentally the coronary collateral flow varies passively with the systemic blood pressure, attempts have been made to improve such hearts experimentally and clinically by drugs and a venoarterial perfusion.

The state of the heavily stressed normal myocardium could be improved with drugs either by increasing its oxygen supply or by using the available oxygen more economically. The major mechanism for increasing the oxygen supply is by increased coronary flow since, normally, the oxygen is largely extracted from blood passing through the myocardium. The drugs would have to promote coronary flow in the heavily loaded normal myocardium in which oxygen usage, coronary flow, and coronary A-V oxygen difference are already at a high level. Whether any drug has the desired type of dilatation (active myocardial vessel relaxation, decreased extravascular compression, minimal increase in metabolism and cardiac work, minimal effect on other vascular beds), and whether it also increases ventricular efficiency remains to be determined. In the normal dog, drugs such as papaverine, nitroglycerin, epinephrine, aminophylline, Coramine, and khellin augment the myocardial coronary flow and oxygen supply, but generally at a considerable expense to the heart through decreased coronary sinus oxygen (with nitroglycerin coronary sinus oxygen is increased), and increased cardiac work and metabolism. In normal man, sublingual nitroglycerin leads to an increased myocardial oxygen usage (increased coronary flow and constant coronary A-V oxygen difference), with little or no change in cardiac output and cardiac work, and with a decreased efficiency (42). In patients at rest, with coronary artery disease, coronary flow is normal. Following nitroglycerin, coronary flow and oxygen usage are unchanged but systemic blood pressure, cardiac work, and cardiac output are reduced; hence, coronary resistance is not changed while efficiency is decreased (138). It would thus seem that the dilator capacity of the coronary tree with coronary artery disease is exhausted. The

mechanism whereby nitroglycerin relieves pain is not that of general coronary dilatation and is unknown.

The incidence of cardiogenic shock complicating acute myocardial infarction has been reported as 12 per cent, and mortality associated with this complication may be in excess of 80 per cent (3, 121). Vasopressor drugs have been widely employed in this situation (see table 1 for details). The improvement that occurs in the human heart with drugs such as neosynephrine and norepinephrine, in the presence of coronary insufficiency and infarction, arises because of a good dynamic response in the normal but overstretched myocardium. This presumably augments the coronary collateral flow by increasing the coronary perfusion pressure and by making the heart smaller (see section on coronary collaterals).

Although the use of vasopressor agents may reduce mortality in myocardial infarction with shock, at least half fail to respond. In such patients, extracorporeal circulatory support is being tried whereby blood is pumped from a convenient vein to an artery (14, 357). The major objective is to produce a sustained increase in aortic pressure and, hence, an increase in coronary, cerebral, and other important regional circulations, and yet, without an increase in left ventricular work that might cause further cardiac deterioration. Conclusive evidence of the benefit of this procedure has not yet been obtained. In dogs subjected to coronary embolization, use of a closed-chest extracorporeal circulation with blood transfer from the veins to the abdominal aorta has been effective in restoring central aortic pressure only if the aorta is occluded beyond the pump (219).

Coronary Artery Collateral Circulation

PREPARATIONS AND METHODOLOGIES FOR COLLATERAL FLOW IN ANIMAL AND MAN. Most studies have been prophylactic in nature, i.e., a potential stimulus has been applied to the normal coronary circulation without interruption of coronary flow to determine whether, following subsequent coronary artery obstruction, the coronary collateral flow will be increased. In only a few instances has the effect on collateral flow of different variables been studied some time after creation of coronary insufficiency. It is unfortunate that a standardized preparation of coronary insufficiency has not been generally employed since this is the situation existing in man with coronary artery disease.

The experimental tools for study of the collateral circulation leave much to be desired. In the experi-

mental animal, these are concerned with measurements of the effects of various prophylactic and, occasionally, postcoronary occlusion procedures on the electrocardiogram, mortality, size of infarcts, exercise tolerance, the coronary artery pressure beyond a region of coronary artery occlusion (the so-called peripheral coronary pressure), and finally, on the injectable and functional collaterals in the presence of coronary insufficiency or occlusion. All are difficult to evaluate because of the considerable variability in the size of the naturally occurring collateral circulation. The latter difficulty can be significantly reduced but not eliminated by using only animals showing large T-wave inversion and S-T segment depression during temporary coronary artery ligation. Experimental indications are that the size of the injectable collateral bed and the level of the peripheral coronary pressure correlate well with direct collateral flow measurements (95). The latter measurement has been widely used and has given considerable information (9, 153). The collateral flow (retrograde or backflow) is determined by collecting the volume of blood flowing externally from a tube inserted into the peripheral end of a centrally occluded coronary artery. This is flow before it has passed through a capillary bed, i.e., it is fully oxygenated, and is presumably somewhat too large because, in the measurement, it drains against atmospheric pressure whereas, functionally, the collateral blood must flow against the peripheral coronary resistance beyond the occlusion. Collateral flow can also be measured under selected circumstances as it enters the myocardium, or after it has passed through a capillary bed and appears in the coronary sinus. This can be done when extracardiac tissue with a vascular stalk has been previously applied to the heart to stimulate collateral development. The collateral inflow can be measured acutely in the open-chest dog by interposing a rotameter in the vascular stalk, or chronically by applying an electromagnetic flowmeter to the extracardiac arterial pedicle. The collateral contribution to the coronary sinus is estimated by measuring the decrease in sinus flow after clamping the potential extracardiac source of collateral flow.

Recent investigations indicate caution in the use of the directly measured collateral flow. *a)* Rb⁸⁶ clearance studies estimate collateral flow as two to three times the directly measured backflow, thus suggesting that in addition to functioning inter-arterial channels, other vessels communicate with the ischemic zone at the arteriolar and capillary levels

(235, 247). This method, however, cannot be used for estimating changes in collateral flow because of the unknown and variable extraction ratio of this substance in the ischemic area. *b)* The small portion (possibly 15%) of left coronary artery inflow not recoverable in the coronary sinus or anterior cardiac veins has been largely accounted for by drainage of the septal artery and some branches of the left descendens into the right ventricular cavity (265). Thus, in the presence of coronary artery occlusion, some blood might perfuse portions of the septum retrogradely during systole when the pressure gradient might be favorable.

Tests of coronary collateral function in life in the normal and diseased heart of man have been largely restricted to monitoring changes in the electrocardiogram to exercise tolerance and angina and, after death, to injection of the coronary collateral circulation at autopsy with opaque viscous material (338). In those individuals with an occluded coronary artery ramus and undergoing a coronary operation, it would appear feasible to use as an index of collateral flow the coronary pressure beyond the occlusion, which can be measured by simple needle insertion. This technique used so successfully in animals has not been attempted in man. Finally, coronary angiographic studies by Sones (352), and others, have demonstrated collaterals in both normal and abnormal hearts. Whether this technique has a future in the study of the development and regression of collaterals and atheromatous lesions remains to be seen (184).

From the preceding it can be seen that, because of our poor methodology, and especially because the direct or indirect measurement of collateral flow has not as yet been made in man, objective evidence of positive benefit to the heart cannot come primarily from observations after experimental or surgical maneuvers or coronary surgery in man, but must come from the effect of various procedures on coronary collateral function in other animals.

NATURAL RESPONSES OF THE CORONARY COLLATERAL CIRCULATION. The natural responses of the coronary circulation of animals during experimental coronary artery constriction and occlusion, which, presumably, also happen in the heart of man, have been studied extensively.

Considerable reduction in the lumen of a coronary artery can occur with minimal or no permanent change in coronary flow. This is so because the coronary resistance to flow measured beyond a point

of occlusion (by ligation) of a left coronary artery branch is considerable, being about 30-20 mm Hg, and the central coronary resistance is quite low (153). The effect of a central constriction on coronary flow is a function of how much the resistance imposed by it is in relation to the resistance in the coronary bed. When the flow to the bed is reduced by central constriction, the peripheral vessels dilate as a result of the associated ischemia and the flow may tend to increase, the combined result of which will be a new equilibrium. Hence, since the peripheral resistance in the coronary bed is constantly changing and will be decreased by the anoxia induced by the central constriction, and since the effect on flow of any central constriction of lumen is a function of how much that resistance is, in relation to peripheral resistance, no predictions can be made as to the effect on blood flow when the coronary artery is constricted by known amounts. Since the peripheral resistance is relatively high, generally sizeable reductions in lumen are necessary before inflow decreases. Thus, the reduction of lumen of a coronary vessel may be of little functional importance to the vascular bed supplied by that vessel when the rate of flow is normal or somewhat low, but the same constriction can seriously limit flow to the same bed just at the time when the requirements of the latter are greatest and flow would otherwise be much greater (153). Obviously, however, this compensatory dilatation of the coronary bed in the presence of constriction of its central coronary artery has a limit, and flow through it will ultimately fall significantly. In part because of this, the heart has a remarkable ability to retain viability of its muscle beyond a constriction, and significant changes in the electrocardiogram do not occur until coronary inflow is reduced approximately 70 per cent (383).

Studies have been made of how quickly such an ischemic area with its potential collateral supply of oxygen becomes nonviable. Admittedly, tests for viability are crude. However, if the criteria used are an absence of local action currents, failure of local conduction, and lack of movement in the presence of generalized ventricular fibrillation, then viability does not usually continue beyond an hour, although occasionally the presence of local action currents and excitability may persist from 2½ to 7 hours (403). The return of normal myocardial function has been studied also after reinstitution of coronary flow in dog hearts maintained anoxic for prolonged periods on an extracorporeal circulation. Hearts maintained anoxic for up to 100 min can maintain their blood pressure on removal from the extracorporeal circulation (65).

Within 1 min after occlusion of a left coronary artery branch, the intracoronary pressure beyond this point drops to about 30-20 mm Hg and useful function is lost, for the muscle now lengthens during systole of the left ventricle (359). When, however, the peripheral end of this ligated coronary artery is permitted to bleed externally, collateral arterial blood appears immediately, averaging about 3.0 ml per min for about 50 g of potentially infarcted myocardium, and this blood can be shown to come from the other nonoccluded coronary arteries (153). The collateral communications are largely in the epicardial areas (40). Probably not more than 2.4 ml of this blood (containing 0.5 ml oxygen) would perfuse the myocardial bed if the collateral flow were not permitted to bleed externally. This is because of the peripheral resistance existing beyond the point of occlusion and averaging 20 or so mm Hg. That most of this calculated collateral flow actually traverses the capillary bed is evidenced by the fact that the electrocardiogram improves when the collateral flow is not permitted to bleed externally (96, 98).

Most of these hearts with occlusion of a major left coronary artery branch die within a number of hours. For example, experimental ligation of the left circumflex coronary artery may give mortalities of 70 per cent or more (170). Other hearts are more fortunate, for if they survive the first few hours, then, for some completely unknown reason, within 12 hours collateral flow starts to rise, doubling within 2 days, and within 3 to 4 weeks it may approximate 40 to 100 per cent of normal inflow into that coronary artery. Almost all the collateral flow comes from the unoccluded coronary arteries. The myocardial fibers which were lengthening early after occlusion now shorten in systole. Concurrently, the peripheral coronary pressure increases to values somewhat less than the normal central coronary pressure and the myocardium shortens during systole (153).

MEANS OF EXPERIMENTALLY CHANGING COLLATERAL FLOW EARLY AFTER CORONARY OCCLUSION. The level of collateral flow with its oxygen content is estimated to be about 40 per cent of that calculated as necessary to maintain indefinitely the viability of this myocardium, since the oxygen uptake of 50 g of a heart with perfused coronary arteries at rest and doing no external work approximates 1.2 ml, as compared to the immediately available collateral oxygen supply of 0.5 ml (249). Hence, it is important to try to increase immediately this collateral flow or backflow. Except for one report on the positive effect of nitroglycerin

(229), this level of backflow has not been made to increase for 8 to 10 hours by drugs or by any known physiological means, such as increased heart rate, increased flow in the other coronary arteries, induction of hypoxia or hypoxemia in the other coronary arteries (204). Why the collateral flow remains fixed, why the anastomoses function as a set of inert tubes, and why they do not exhibit vasomotion or participate in the vasodilatory response of the normal coronary bed are not known. This situation contrasts with the rapid development of collaterals in other vascular beds such as the femoral and carotid arteries (153).

This retrograde flow can, however, be greatly reduced by excessive stretch of the myocardium and reactive hyperemia in the other nonoccluded coronary artery branches. The improvement that occurs with drugs such as neosynephrine and norepinephrine in the human heart in the presence of coronary insufficiency and infarction could result from an increase in the oxygen supply to regionally ischemic muscle (337), and from augmentation of the collateral flow through increase of the coronary perfusion pressure and a smaller heart size. Spasm of the coronary arteries with diminished blood flow is also frequently invoked to explain the onset of episodes of angina pectoris and of reduction in collateral flow. However, no firm conclusion can yet be drawn as to whether flow in one coronary artery can be influenced reflexly and adversely by impulses arising from an intra- or extracardiac source (see the section on Reflexes).

Lysis of coronary thrombi induced experimentally can be observed to follow fibrinolytic therapy. Whether this will change the evolution of early myocardial infarction and result in salvage of ischemic tissue without collateral development has not yet been determined (276).

RESPONSE OF THE CORONARY COLLATERAL CIRCULATION TO NATURALLY OCCURRING PROPHYLACTIC STIMULI. As indicated earlier, the intercoronary arterial communications are generally small in normal man, fewer than 10 per cent having anastomoses with diameters of 40 μ or more (39). However, others using corrosion and injection techniques found anastomoses of greater size and with greater frequency (18, 226, 371). The coronary arterial tree of the pig is strikingly similar to that of man (96, 289), while in the dog the anastomoses are larger and more frequent. These differences in collateral function might be explained on a technical basis or as fundamental species variations; however, they could be related to the types of

collateral stresses to which the hearts have been previously exposed.

Evidence, largely from the classical work of Zoll *et al.* (411), indicates that the incidence of injectable coronary artery collaterals is quite small in normal human hearts, but is greatly increased in the presence of coronary artery constriction or occlusion. There is also evidence in different species that nature adopts prophylactic measures to protect some hearts against subsequent coronary artery occlusion. The coronary vessels appear to be capable of setting up or enlarging anastomoses between themselves without the stimulus of coronary occlusion or insufficiency. Presumably, this is due to some form of antecedent stress. In these hearts, stresses, some known but mostly unknown, prophylactically enhance the potential collateral circulation without the stimulus of coronary occlusion or constriction. These are exemplified in man by the increase in the incidence of the injectable coronary arterial collateral bed in the presence of hypertrophy, valvular disease, cor pulmonale, anemia, and probably high altitude (38, 412; also Rotta, personal communication). This is exemplified in the pig by an increase in the injectable collaterals in the presence of anemia (39, 412), and in the dog by an increase in both the injectable and functional collaterals in the presence of high altitude (Rotta, unpublished observations), and transfused anemia (97). No good experimental evidence exists, however, to indicate that physical exercise per se augments prophylactically the collateral flow as measured in a normal coronary artery immediately after its occlusion. The injectable coronary collateral bed, however, is stated to increase in exercised rats (360). Individuals who escape serious consequences from coronary occlusion may well be those whose collaterals have been previously expanded by such means.

MEDICAL, PHYSIOLOGICAL, AND SURGICAL ATTEMPTS TO IMPROVE THE CORONARY ARTERY COLLATERAL CIRCULATION PROPHYLACTICALLY. Either before or after establishment of coronary insufficiency, it should be possible to improve the state of the heart of dog or man by augmentation of the coronary artery collateral circulation which naturally functions, by retrograde perfusion of the ischemic coronary bed with arterial blood, or by elevation of the ventricular fibrillation threshold. In man, in addition, positive and subjective benefit could arise through psychogenic effects which are not necessarily related to the heart.

Chronic experiments have produced no good evidence to indicate that any drug promotes collateral

flow or reduces the size of infarcts produced by subsequent coronary artery ligation (380, 404). The alleged favorable effect on survival of the use of drugs such as papaverine or quinidine is better explained by their known action in raising the fibrillation threshold and in reducing myocardial excitability (384).

The capable experimental coronary surgeon has been able to improve considerably on the state of such hearts. Much of the advancement in the surgical and physiological fields has arisen from the pioneer investigations and stimulus of Beck (19, 50, 255). The procedures used include section of the cardiac sympathetic nerves (178), induction of myocardial hypoxia by various manipulations of the coronary venous system or by a coronary fistula (19, 79, 95, 158), production of mechanical and chemical pericarditis between the epicardium and pericardium to use the extracardiac anastomoses (19, 178), application of extracardiac tissue to the heart (271, 324, 372, 373), internal mammary artery ligation (99), sham operations (1, 19, 85), coronary endarterectomy (241, 326), and coronary artery bypass (171).

Many of these procedures in the experimental animal are of positive benefit to the heart and give immediate or sustained protection against subsequent ligation of a major coronary artery ramus. Ligation of a major ramus of the left coronary artery causes about a 70 to 90 per cent mortality within the first 1 to 2 hours, and chronically there is considerable infarction (95). When partial or complete occlusion of the coronary sinus precedes coronary artery ligation, or when a portion of the coronary bed is perfused in retrograde fashion by connecting the coronary sinus to an artery, the immediate mortality is reduced considerably. With the exception of section of cardiac sympathetic fibers and internal mammary artery ligation, most other procedures—chronic coronary venous maneuvers, application of various chemical and mechanical irritants, separately or in combination, and application of extracardiac tissue to the heart, generally lead to a significant reduction in mortality and infarction (there are, however, exceptions) (124). There is an increase in the injectable and functional collaterals with the chronic coronary venous maneuvers and with the application of mechanical and chemical irritants to the heart. The level of collateral flow, 5 to 12 ml in most instances, considerably exceeds the control retrograde flow of 3 ml with acute artery ligation alone. Accordingly, it is deduced that these surgical maneuvers give sustained, and in the case of the coronary venous maneuvers, immediate protection against ligation of a

major coronary artery branch. The retrograde flow in the chronic experiments equals or exceeds that estimated to be necessary to maintain viability.

Cardiac benefit from these procedures could arise from retrograde flow of blood from the superficial veins through the capillary bed, from development of intra- and extracardiac collaterals, or from elevation of the ventricular fibrillation threshold, thus giving nature time to develop additional collaterals to sustain the heart. There are no critical experiments to prove that with the acute coronary venous maneuvers, protection against fibrillation and death is supplied by blood flowing in a retrograde direction from coronary vein to capillary to ventricular cavity. Acute perfusion of the coronary sinus with arterial blood at or near aortic blood pressure, or acute ligation of the coronary sinus, results in venous congestion of the left heart with an increased coronary venous pressure, at times equal to the aortic pressure, a diffuse myocardial hemorrhage (with the exception of the septum which remains pink in color), and a sizeable reduction in left coronary inflow and cardiac output. When the peripheral portion of the occluded coronary artery is permitted to bleed externally, the measured backflow is of highly reduced blood and the volume is increased greatly (to 15 ml or more) over that which occurs with acute coronary artery ligation alone (153). It is very important to know that this blood can be shown to have traversed the capillary bed of the occluded coronary artery in a reverse direction. However, proof is lacking that, when the ligated coronary artery is not permitted to bleed externally, flow from the superficial coronary veins is diverted through the capillary bed of the left myocardium and then into the left ventricular cavity. Actually, the development of extreme myocardial embarrassment, together with the fact that most of left coronary artery inflow and the blood entering the coronary sinus from the shunt can now be recovered in the anterior cardiac veins of the right ventricle (153), offers not quite certain evidence that the deep ventricular drainage channels are not used. However, the high values for venous pressure in the coronary sinus and the augmentation of peripheral vascular pressure and retrograde flow which appear in the left coronary artery immediately after left coronary venous ligation decrease after a time interval (up to 30 days) to values only slightly above normal (153).

The observation that these procedures can elevate the ventricular fibrillation threshold suggests but does not prove that this is a major mechanism of protection. In hearts with chronic application of these

various latter maneuvers, protection in large part, and in many instances, is probably afforded by the augmented collateral circulation. For example, with an aorta-coronary sinus shunt, the backflow of 10 to 12 ml of arterial blood exceeds that calculated to be necessary for viability and persists for at least a year and even after loss of function of the shunt (95). But since most hearts following coronary artery ligation die within 24 hours, since the usual retrograde flow observed with these procedures is not large, and since sham operation involving manipulation of the heart at times increases collateral flow or gives sustained protection against coronary occlusion, or both, the possibility must be entertained that there may be no specific effect of some of the maneuvers; they may act by raising the ventricular fibrillation threshold thus giving time for collaterals to develop.

In some procedures that apply extracardiac tissue to the heart, such as a pedical skin flap (271), or an internal mammary artery ligation (99) or its myocardial implantation (324), the collateral flow does not increase. These studies, however, are incomplete. Further work should be done to determine, in addition to the usual arterial collateral flow measurements, whether blood actually flows from the extracardiac tissue through the capillary bed of the myocardium into the coronary sinus or other coronary venous outflow channels. Despite some positive findings, no firm conclusion can be drawn (372, 373).

ATTEMPTS TO IMPROVE THE COLLATERAL CIRCULATION AFTER CORONARY ARTERY OBSTRUCTION IN ANIMALS AND MAN. As already indicated, immediate or early augmentation of the coronary collateral circulation, beyond that occurring naturally following marked coronary constriction or occlusion, has not been demonstrated. Neither experimental estimation of a favorable delayed or chronic collateral response (decrease in infarct size and increased injectable collateral bed or collateral flow) to drugs has been demonstrated (379, 412). However, the following evidence of positive benefit has been reported: *a*) Treadmill exercise, when added to a pre-existing coronary insufficiency, appears to increase the collateral flow to a level greater than with coronary constriction alone (98). *b*) In the presence of aneurysm-induced chronic left coronary insufficiency and epicardectomy, the addition of a mammary artery implant or application of an Ivalon sponge is stated to greatly extend the survival time of the dog and to increase the functional communications of the ischemic bed with the left ventricular cavity and

extracardiac arteries. This benefit does not follow the use of cardiopneumopexy or the applications of various other irritants to the myocardium (374). *c*) Experimental attempts have been made to improve the blood supply to the normal heart and the heart with infarction (intracoronary injection of plastic microspheres) by altering the time of arrival of the arterial pressure pulse so that the systolic pulse arrives during diastole, the period of greater flow (59, 188, 203). The procedure is reported to greatly reduce the mortality rate from the myocardial infarction and to increase the injectable collateral bed. *d*) When a pulmonary artery to left atrial shunt is added to an already existing chronic occlusion of the left circumflex branch, coronary angiograms and vinyl acetate casts show a more rapid collateral filling and a greater vascularity, respectively, than following coronary artery occlusion alone (30).

Most of the procedures designed to promote collateral development, including the sham operation, have been applied to the heart of man suffering from coronary artery disease. All appear to increase to some extent the work and exercise tolerance and to decrease cardiac pain (19, 178, 374). The summary of over 600 patients on whom the Beck operation was performed may serve as an example (51). These observations are not necessarily explained on the same basis of the improvement in the collateral circulation of the dog which follows such procedures. This is because in the dog most surgery precedes coronary artery ligation and is designed to promote collaterals in the presence of a normal coronary circulation, whereas, in the human, surgery follows coronary artery occlusion and is designed to promote collateral circulation after the coronary insufficiency has been naturally established. In man, hypoxia, the greatest known vessel dilator, and a natural stimulus to collateral development, has already been working for many months. Since human coronary surgery which follows coronary occlusion has as yet little counterpart in animal experiments, attempts should not be made to interpret these human coronary experiments on a physiological basis.

The explanation of the results in man is not clear. Patients treated surgically by epicardial phenolization, poudrage, cardiopneumopexy, and bilateral internal mammary artery ligation, although showing marked relief of angina, do not show electrocardiographic improvement or an increase in coronary flow, or a decrease in coronary vascular resistance following nitroglycerin (44). Undoubtedly, some subjects are protected and live longer because of the known experi-

mental fact that handling the heart raises the ventricular fibrillation threshold. Some may be improved by procedures such as de-epicardialization which could obliterate the afferent pathways for pain. However, results of the sham operation of Adams (1) and Dimond (85), involving only a skin incision, strongly suggest that much of the positive benefit is on a psychogenic basis.

Coronary endarterectomy which has been applied to man is on a sound physiological basis and its purpose is entirely different from the preceding. The surgeon directly reestablishes coronary flow through the original coronary artery by removing its atherosclerotic plug. It does not require collateral development and should be effective provided there exists a gross coronary insufficiency of blood beyond the obstruction, provided the vessel remains patent and thrombi do not form, and provided there are no sizeable atherosclerotic lesions beyond the region of the occluded coronary artery. It is quite doubtful that these criteria can be met (182). Preliminary experiments with the use of endarterectomy for coronary occlusion were apparently initially favorable to the patients, relieving their angina, and improving their electrocardiograms and work tolerance (241, 326). However, most of these patients have died, and no evidence is available that at autopsy the endarterectomized artery has remained patent. Many more operations will have to be performed to establish the possible merit of this procedure in humans.

Finally, bypass of a length of an occluded coronary artery by anastomosis of its peripheral patent end to a systemic artery has not yet been attempted in man.

In dogs, a nonsuture anastomosis by intima-to-intima contact between the left coronary artery and the left internal mammary artery has been highly successful (171). In almost all the dogs (24 of 33), the anastomoses have been demonstrated to be patent and without myocardial infarction as evidenced by gross observation, angiography, and measurement of coronary blood flow through the anastomosis up to the time of dog sacrifice (12–24 months after operation). Other technical achievements in this area include chronic anastomoses of two branches of the left subclavian artery to the peripheral and central ends, respectively, of the left circumflex coronary, the central end of the main left coronary being tied (unpublished observations), and end-to-end anastomosis of the central end of the main left coronary artery to the peripheral end of the left subclavian artery (251). Since anastomosis of a coronary artery branch to a systemic artery is almost always successful in the dog in which the anastomosed vessels are only 2 to 3 mm diameter, there should be no difficulty at all in the human heart in which the coronary artery branches have a much greater diameter. This procedure might, therefore, have an application in the creation of a permanent new blood supply in the presence of coronary artery disease in man. One should not, however, overlook a probably late complication to successful coronary endarterectomy or coronary bypass in man. In the presence of such a large new blood supply, the existing collateral flow will disappear. If another coronary occlusion subsequently occurs, the patient will be in difficulty, having lost his collaterals.

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Maternal blood flow in the uterus and placenta¹

S. R. M. REYNOLDS

Department of Anatomy, University of Illinois College of Medicine, Chicago, Illinois

CHAPTER CONTENTS

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AMONG THE SEVERAL ORDERS of mammals, no organ in the body is more varied in form and size than the uterus. One may not properly speak of "the uterus" as an organ in which identical physiological activities take place in the fulfillment of the purpose for which a uterus exists. True, the uterus permits implantation of fertilized blastocysts, accommodates the products of conception for a normal span of development, and then delivers to the outside world an organism or organisms that can survive. Specialized adaptations exist among mammals in the form and function of the various uterine and placental types. Such variations in uterine and placental structures, coupled with specialized variations in cyclic activity, serve to render them quite different from one another while achieving a common goal, namely, the production of living offspring.

As a student of physiology, man tends to be an-

thropocentric; he employs many kinds of animals exhibiting many types of mechanisms but, while examining comparative basic processes, he hopes to understand himself. It is necessary, therefore, that insofar as present knowledge permits, the several types of form and function be considered.

COMPARATIVE ANATOMY OF UTERI

It is axiomatic in developmental biology that ontogeny repeats phylogeny. This is to say, as one passes from species A to species Z there are grades of morphological complexity that can be seen. Similarly, in the development of species Z, all or most of the essential elements of species A, B, C, D, . . . Z are observable in transition from a simple type to a complex type of structure. Although this is an oversimplification of the situation, it is generally true and it is as easily demonstrable for the uterus as with any organ in the body [Reynolds (198)].

Like so many viscera of the body, the uterus may be characterized as starting as paired symmetrical tubes, part of the mullerian duct system. In monotremes (e.g., Echidnae), marsupials (e.g., Marsupialae), and some rodents (e.g., Leporidae) at least, two uteri remain separate throughout life, arising cephalad at the caudal end of the fallopian tube and terminating caudally with independent cervical openings in the vagina. In other species, the caudal ends of the ducts fuse mesially to form a single cervical opening in the vagina. Examples of this are seen in certain rodents (e.g., *Mus rattus* and *norvegicus*), carnivores (e.g., Canis), ungulates (e.g., Ovis, Bovis, and Equidae) and many others. Continuing the extent of mesial fusion to the ultimate degree, the primates normally have a single uterus, which receives two fallopian

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tubes, and a cervix. These several types of uteri are recognized as the uterus duplex, the uterus bicornis, and uterus simplex; the latter representing, paradoxically, the most complicated organization of all, being, as it is, the fusion of paired simple ducts into a single complex organ. Just as increasing degrees of complexity of organization may be seen throughout the phyla so, in the development of the uterus simplex, all the transitional stages of development from the duplex to the simplex form are recognized. Persistence of incompletely formed uteri as malformations sometimes complicates the parturitional process. No one has produced experimentally arrested fusion or partial development of the uterus simplex, probably for the simple reason that no studies of experimental teratogenesis have been made in primates.

Since the several classes of uteri have in common an orderly and progressively more complex organization, one might anticipate that there would be an

orderly and progressively more complex organization of the vasculature of the uterus among different animals. So there is.

ANGIOGENESIS IN THE UTERUS

All organogeny takes place around a primary vascular organizational pattern [Evans (71)]. Blood vessels begin as a diffuse capillary network, some channels of which become more and more prominent, larger and structurally more complex as arterial and venous pathways come into being [Thoma (233)].

Why this is so is not clear, although Thoma has postulated that the process is governed in part by the hemodynamic load imposed upon certain parts of the delicate capillary system. As these pathways become more defined, they give rise to still further differentiation of more peripheral branches. The sizes and angles of these branches are related to certain physical relationships that were first laid down by Hess (105) on thermodynamic grounds, and first given substance experimentally by Reynolds (197) in the developed vascular tree. However, more than simple hemodynamics is involved, since Price (177) has shown that organogenesis can take place in tissue culture only if a semisolid medium is used, but not if a liquid medium is employed. Thus the dependence or role of vascular development as a contributory mechanism to organogenesis is seen to be unessential for primary organization, but to be essential for subsequent development.

VASCULAR CONNECTIONS OF THE UTERUS

The common vascular denominator for all uteri is the pattern of vascular supply of blood to, and drainage of blood from, the uterus. This was certainly seen by Aristotle, by Vesalius, and by Hunter. It was not stressed as a vascular complex, apparently, until the early part of this century by Byron Robinson (211). This author compared in different species the vascular circle that starts in the aorta by way of the anterior division of the internal iliac arteries on each side, or may arise in common with the vaginal, umbilical, or middle rectal arteries. The uterine arteries descend in the fat at the base of the broad ligament and, going between the layers of that ligament, pass to the uterus, following a tortuous course. They run along the mesial sides of the uterus, giving off branches to the body of the uterus along the way. At the cephalic end

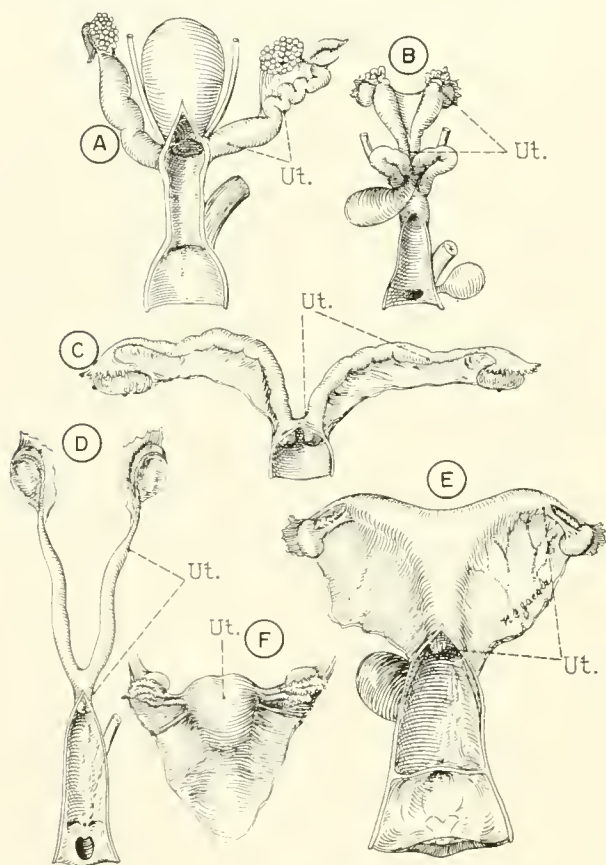


FIG. 1. Comparative types of uteri from the uterus duplex to the uterus simplex found in various mammals: A, monotreme (*Echidna aculeata*); B, marsupial (*Didelphis virginiana*); C, rodent (rabbit); D, carnivore (dog); E, ungulate (mare); F, primate (*Macacus rhesus*). [After Rudolph and Ivy, taken from Reynolds (198).]

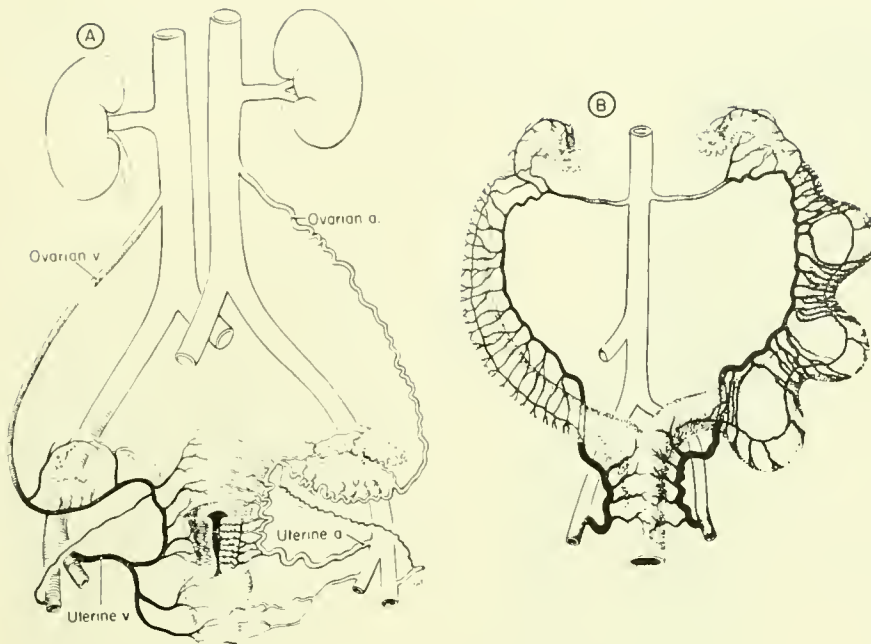


FIG. 2. Arrangements of arterial and venous pathways to uterus simplex (*left*) and uterus duplex (*right*). The "circle" of the arterial pathway is shown as a continuous pathway from the aorta, ovarian artery, uterine artery, hypogastric artery (uterus simplex), femoral artery, and aorta. A similar circle exists in the venous connections. [After Byron Robinson (211).]

of the uterus, the arteries anastomose with a branch of the ovarian artery, one on each side. The uterine arteries supply, therefore, part of the vagina, the uterus, and fallopian tubes on each side.

Since the ovarian arteries arise from the aorta just below the renal arteries, it will be seen that there is, indeed, a large communicating arterial circle supplying the uterus on each side of the midline. In the case of partial or complete uterine fusion during development there is further connection of the finer arterial branches from both sides in the body of the uterus [Faulkner (77, 78)]. The arcuate arteries of the uterus lie in the zona vascularis in the myometrium. Myomas in the smooth muscle of the uterus are singularly deficient in blood supply (see fig. 3) [Faulkner (77), Holmgren (113)].

We observe in this arrangement that the uterus simplex is supplied from two primary arterial sources, on each side, and that where the form of the uterus permits, there is free union between these. It is possible to see that the uterus, which increases along with its blood vessels many times over in size during gestation, is assured of a reasonably large and constant head of arterial pressure at all times.

The morphology of the venous drainage of the uterus is equally important for the physiological changes that take place in the uterus and its circulation. The uterine veins, without valves, arise from within the tissues of the uterus and enter the broad ligament at numerous points in increasingly large

venous channels as smaller ones have united along the way. However, there are four main venous paths of exit from the uterus [Bieniarz (31)]. In the common laboratory animals, the veins of the broad ligaments unite and form rather uncomplicated plexuses in the broad ligament [Reynolds (198)] receiving veins from the uterus along the way. The parametrial veins join with ovarian veins to drain blood toward their point of entrance into the inferior vena cava on the right side and the renal vein on the left side.

As with many parts of the venous system, the drainage connections are complex, rather than diagrammatically simple as is commonly believed. In the primate, these relations are more complicated than in the usual laboratory animals. For example, in the broad ligament of primates, there is an extensive pampiniform plexus, having multiple connections with the pudendal veins, the several rectal plexuses, the internal iliac veins, and inferior vena cava. Not only may uterine blood move toward the heart through the inferior vena cava, but through the internal and superficial epigastric veins to the mammary and internal costal veins as well. Blood may also, if pressure within or upon the venous system requires it, flow to the ascending lumbar veins, by way of segmental connections, to the azygous and hemiazygous veins.

The ovarian vein enlarges greatly during pregnancy [Borell & Fernström (38), Hodgkinson (110)]. There is much current interest in this subject, first stressed



FIG. 3. Arterial pattern of uterus. Cleared preparation. One small myoma on right side. [From Faulkner (77).]

by Davidsohn (64) many years ago. Further assurance of venous return exists by way of multiple venous connections to the vertebral vein system, as Batson (27, 28) has emphasized (see also Jeffcoate (117)). The ovarian "vein" in part is in reality the tubo-ovarian pampiniform plexus which pours blood into the inferior vena cava from the right side, or the renal vein on the left. Other interconnections exist, also. However, sudden occlusion of the inferior vena cava can cause separation of the placenta [Mengert *et al.* (150)]. Donnelly (66) relates noninduced placental separation to gross abnormalities of the placenta.

All in all, within the uterus itself and in the venous systems of the abdominal cavity and body wall, there are abundant intercommunications, so that opportunity for obstruction to the venous drainage of uterine blood is minimized. Barcroft & Rothschild (21) emphasized this with regard to the rabbit; Bieniarz (31) has stressed it in relation to the human. Oughtred & Reynolds (165) demonstrated the operation of the

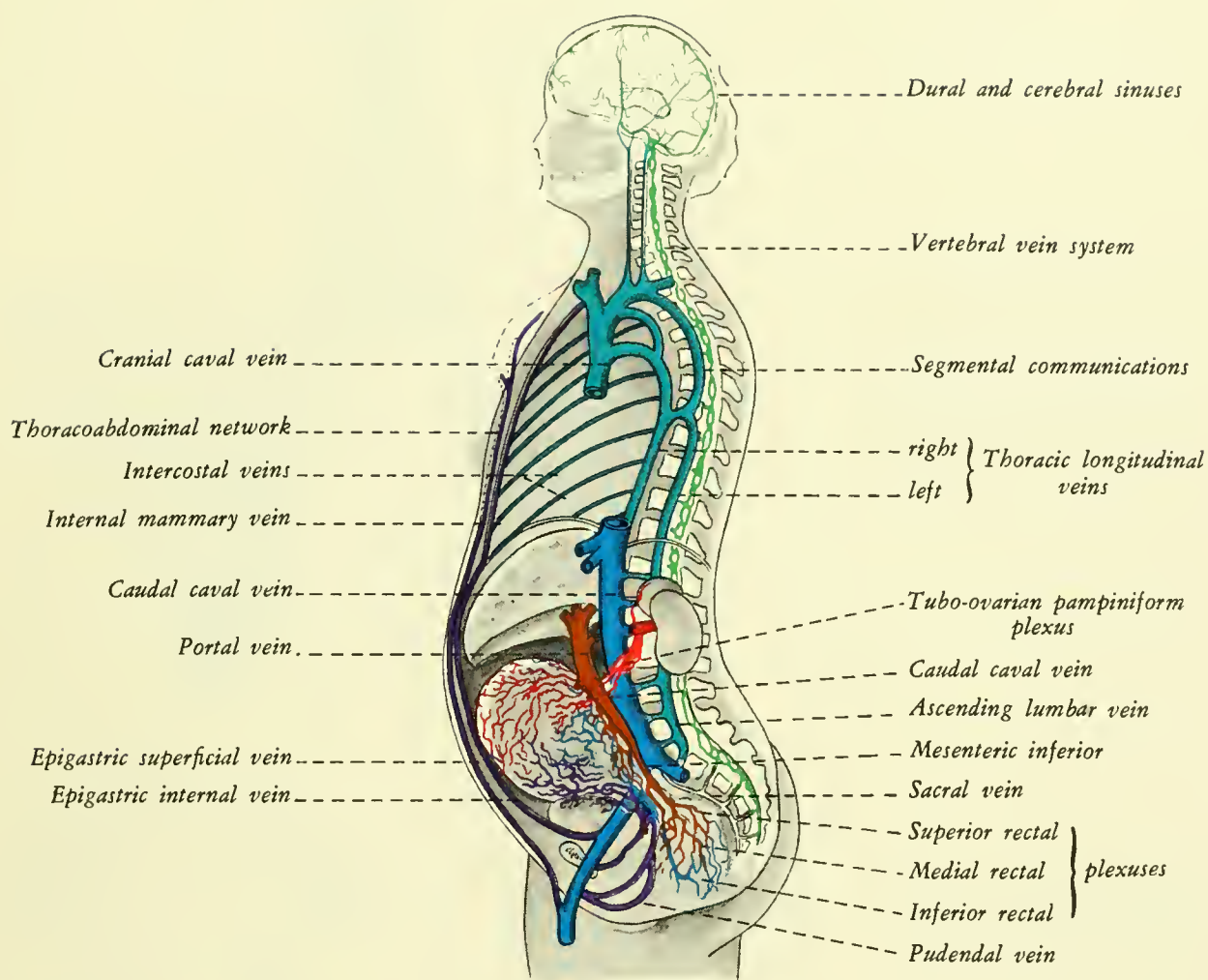
collateral abdominal and somatic venous systems in the dog when the inferior and superior vena cava were blocked at various levels.

FUNCTIONAL IMPLICATIONS OF VENOUS DRAINAGE

Problems that arise from malfunctioning of the venous system are recognized. In general, they are twofold. In animals having an erect posture, at least in the human, pelvic congestion which is correctable by operative procedures is known [Taylor (230), Curtis *et al.* (58)]. These contribute to endocrine disorders and a variety of clinical entities. The second group of functional disorders is related to distribution of the vascular loads upon the circulatory system in late pregnancy [Bieniarz (30)]. When the placenta in the human is implanted high in the uterus, drainage by way of the ovarian pathways predominates. When this happens, albuminuria, hypertension, and even toxemia frequently occur. A continuous discharge of several hundred milliliters of blood per minute into the vena cava or renal vein may complicate renal and adrenal blood flow, Bieniarz (31) postulates. Ligation of the vena cava above the renal veins affects renal function and possibly adrenal gland activities as well [Karacv (126)]. When, on the other hand, the placenta is implanted low in the uterus simplex, placenta praevia and hemorrhage more commonly occur [Bieniarz (30)]. The former condition is more frequent in primigravidas, the latter, in multiparas.

Although ovarian vein physiology has been implicated by deduction in the incidence of toxemia [Bieniarz (30)], other mechanisms are suspect, also. Placental ischemia as a factor is considered by Page (168). Saito (214) produced toxic signs in animals with human placental extracts and this is said to be an allergic reaction by Lin (136) who sensitized rats to placental tissue by injection of placental tissue 5 months before. However, killing of the fetuses in hypertensive rats leads to lowering of blood pressure [Page (166)]. Examining the problem experimentally, Ogden *et al.* (162) placed Goldblatt clamps on uterine arteries in pregnant rabbits and observed that progressive hypertension developed promptly. This was relieved by removal of the clamps. Grollman (87) observed that induced hypertension in rats is reduced by normal pregnancy, but not by pseudopregnancy. (See below discussion of the placenta as an A-V

FIG. 4 (facing page). The uterine drainage system during pregnancy (sagittal view). Different visceral and parietal venous drainage routes are shown in different colors. [Reprinted by permission from Bieniarz (31).]



- Caudal caval system.
- Uterovenal visceral circulation.
- Portal circulation.
- The anterior parietal abdomino-thoracic communications.
- Retroperitoneal and retropleural communications to the cranial caval system.
- Vertebral vein system to the cerebral sinuses.

FIG. 4. See legend on facing page.

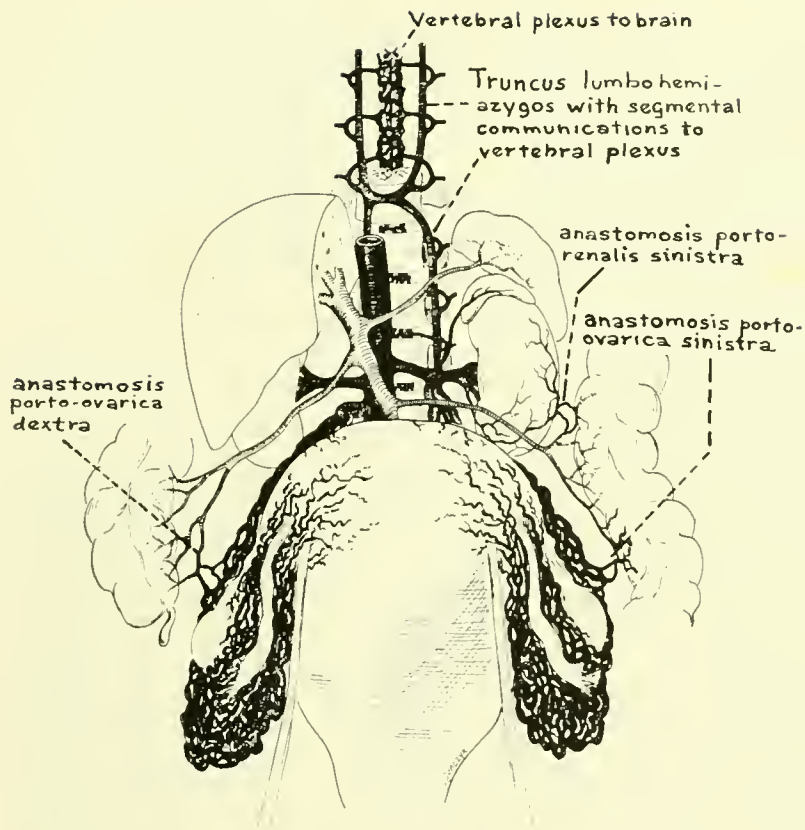


FIG. 5. The uterine drainage in advanced first pregnancy, with predominantly high fundal drainage through the pampiniform plexuses and ovarian veins toward the kidneys, and through visceral and segmental communications, toward the portal circulation, vertebral plexus, and brain. [Reprinted by permission from Bieniarz (31).]

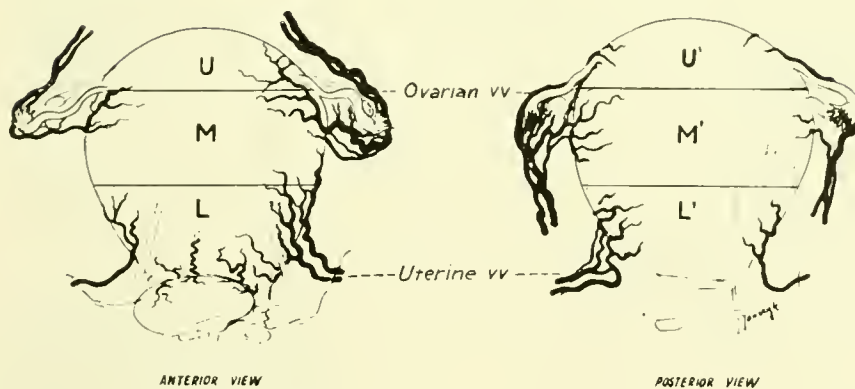


FIG. 6. Anterior and posterior view of the uterus with the venous vascular patterns visible during cesarean section and with regions of placental location. *U'*, upper; *M'*, middle; *L'*, lower portion of uterus. [Reprinted by permission from Bieniarz (31).]

shunt.) A more comprehensive discussion of this subject will be found elsewhere [Reynolds (198)]. It should be noted that there is no logical reason why either the ovarian vein hypothesis or the placental ischemia hypothesis as an etiological factor excludes the other.

The above assertion of morphological and clinical facts makes it clear that the change and distribution of blood flow within and from the pregnant uterus is governed in part by the site of placental implantation, in part by the change in size of the uterus, and in part by the increase in quantity of functional uterine

tissue during pregnancy. Local or regional blood flow is associated with the supply of blood to the uterine tissues and especially to the placenta.

COMPARATIVE ANATOMY OF THE PLACENTA

As with the above discussion of the uterus, it is necessary to recognize that there is a wide array of placental forms. Although Mossman (158) has described these forms and noted their arrangements throughout the several orders of mammals, insufficient

emphasis has been laid upon the demands which these several arrangements impose on the circulation. Further, just as there are differences in gross morphology, so there is still further variation in the microcirculatory organization of the various types of placentas. The generally recognized distinctions in this regard are those of Grosser (88) who classifies placentas on the basis of the number and type of tissue layers interposed between the maternal and fetal bloods. The beauty of this system is that things fall neatly into place. For example, the epitheliochorial type of placenta suggests that in general there are six layers of tissue (maternal endothelium, connective tissue, and epithelium apposed to layers of fetal epithelium, connective tissue, and endothelium). The simplest hemochorial placenta has only fetal epithelium, connective tissue, and endothelium between the two bloods. Intermediate between these two extremes are the syndesmochorial (lacking maternal epithelium) and the endothelial chorial (lacking the maternal connective tissue and epithelium).

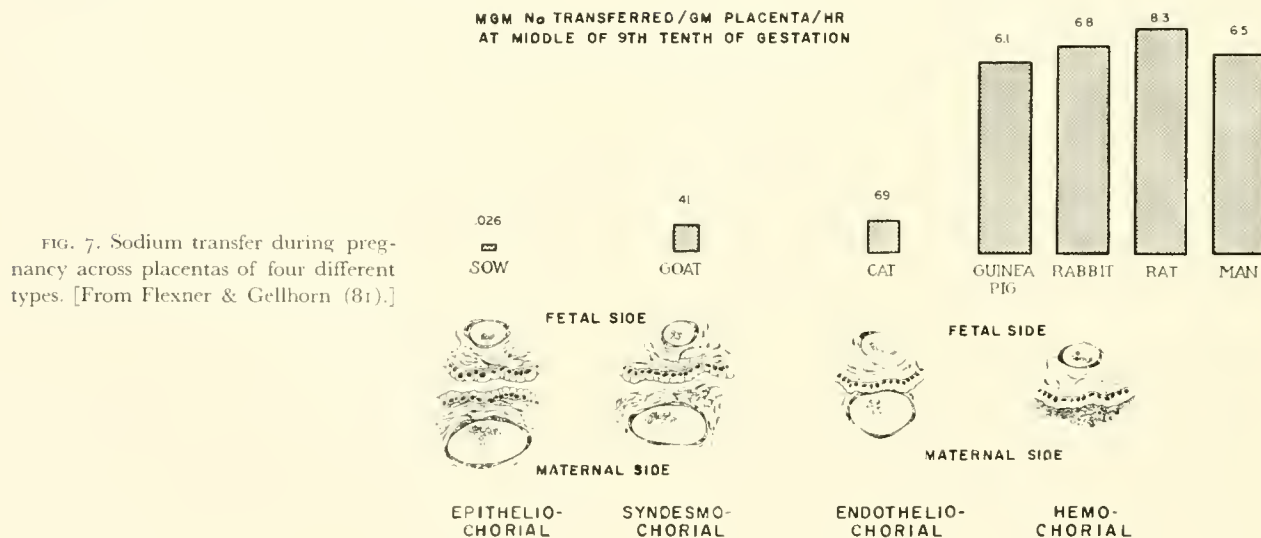
To complicate the apparent simplicity of this system, there is no phylogenetic relationship between the several types of placentas. Some rodents and primates have hemochorial, and ungulates have epitheliochorial and syndesmochorial types of placentas. Carnivores do not fit into any one group. More disturbing to the simple view of Grosser (88) that a neat classification of placental types exists which is based on their microcirculatory relationships is the fact that careful re-evaluations by placentologists in recent years suggest that structural changes take place throughout the life span of the placenta; the morphology is not uniformly constant with regard

to the tissues mentioned above [Amoroso (4), Huggett & Hammond (116)]. Amoroso has enumerated a wide range of types and patterns of changes of vascular arrangements, not only in commonly used laboratory animals but in unusual ones as well. It is found that capillaries "migrate" into intraepithelial locations. One does not find any critical limitation of effectiveness in the transfer of metabolites across the various "types" of placentas in terms of growth and survival of fetuses.

TYPES OF PLACENTAS

Just as there are distinguishing microscopic morphological and physiological differences in the placentas of the various species, there are wide differences in the forms of placentas [Mossman (158)]. Apparently the simplest form is the discoidal placenta, representing a single structure. This is seen in such widely different species as hamsters, mice, rats, rabbits, guinea pigs, and humans, to name a few. The opposite extreme is seen in the placental structures of sheep, goats, cows, mares, and many other species, all ungulates. In these, each developing embryo has a complement of twenty or more discrete discoidal placental parts, called cotyledons, each supplied by a branch from one or two umbilical arteries and drained by a vein that ultimately enters one of two umbilical veins. These cotyledons have vascular connections with others and lie scattered throughout the entire interior surface of the uterus.

Other types of placentas exist. In rhesus monkeys there are two discoidal placentas, one lying on the



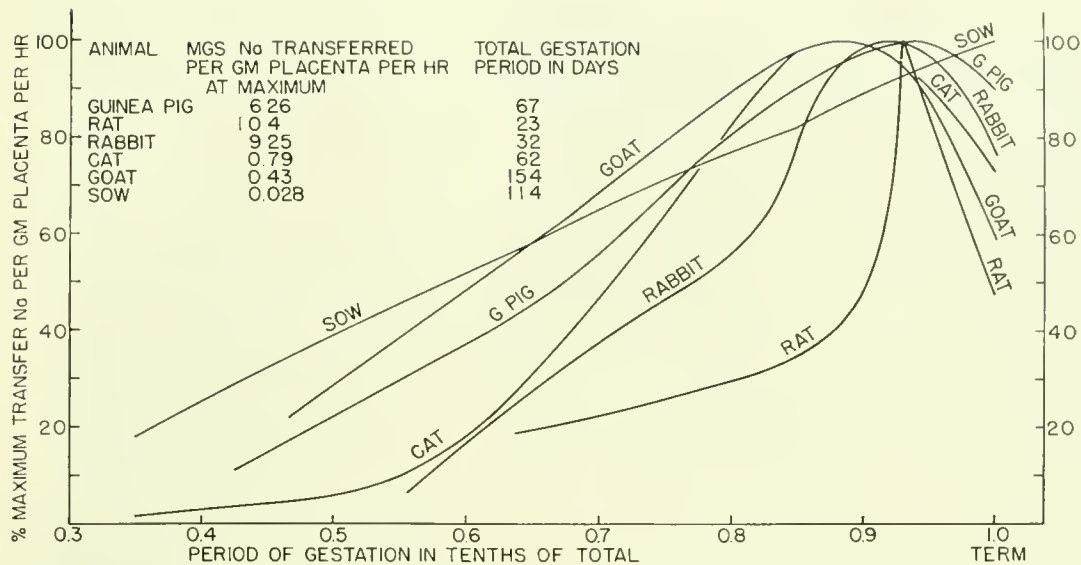


FIG. 8. Transfer rate of sodium during gestation in six species. [From Flexner & Gellhorn (81).]

ventral, the other on the dorsal aspect of the interior of the uterus. However, only one of these receives the umbilical vessels and is called, therefore, the primary placenta. The secondary placenta receives its vessels from continuations of a number of umbilical vessel branches on the chorioallantoic surface of the primary placenta that pass between the amnion and chorion laeve to the secondary placenta, rather like the connection between the cotyledons of the ungulate placenta.

The "unitary" structure of the fully developed discoidal placenta of the human, rhesus monkey, and other species is the cotyledon [Wilkin (245)]. This is a vascular unit which is fetal (see further discussion below). By implication, the maternal placental structures are fitted to the cotyledon. In a sense they are. The decidual plate with its septa blocks off smaller areas of the fetal portion of the placenta as ridges or folds of tissue about a number of the cotyledons. However, the ridges of the septa do not make connection with the fetal tissues in a way that makes discrete, unitary compartments, or chambers. The maternal vascular compartments interconnect deep in the placenta beneath the chorioallantoic plate of the placenta, so that there is a continuum of the maternal vascular area. The entire area is spoken of as a maternal lake or intervillous space. To the extent that there is continuity, this is true, but there are innumerable attachments of fetal vessels covered with chorionic tissue to the basal part of the placenta in the lake on the decidual plate and on the septa

[Wilkin (245)]. The crypts or pockets between septal folds become more numerous as pregnancy advances.

In early pregnancy, isolated lakes of maternal blood in the trophoblast merge and fuse as one may imagine pockets of gas in aging cheese might fuse to form larger pockets. This involves the entire syncytial trophoblast in the area of implantation, embedded in the decidua basalis. As the placenta enlarges and undergoes morphogenesis and the uterus enlarges *pari passu*, the characteristics of the placenta change until it is complete in form, after the fourth month of pregnancy. Only a small proportion of the interior of the uterine surface then is involved. Zonary placentas completely surrounding the fetus are found in some species. These and still other patterns of gross structure and vascular arrangements have been described by Mossman (158) and by Amoroso (5).

Because there is such a variety in the types of placentas and since these undergo important structural changes during pregnancy, a physiologist who measures uterine blood flow during pregnancy may not properly speak of blood flow except as the latter relates to an evolving set of morphological relationships with respect to a given form of placenta. It is to be borne in mind also that the largest part of the gravid uterus is not associated with the placenta; it, too, must be supplied with blood. There are, in a sense, two uterine blood flows, one to the placenta in its various forms, the other to the uterine tissues which are undergoing enormous growth, stretching and change of shape. To measure total uterine blood flow

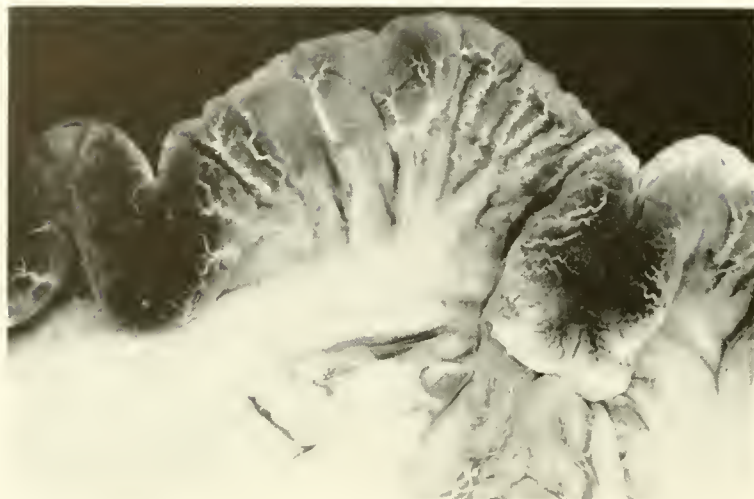


FIG. 9. Circumferential arteries of nonpregnant rabbit uterus. These anastomose with each other laterally and supply the uterine wall. [From Reynolds (199).]

tells what the circulatory load of the gravid uterus is on the maternal cardiovascular system but it fails to tell how this is related to supplying fetal needs, on one hand, and uterine tissue needs, on the other.

PLACENTAL STRUCTURE AND PLACENTAL EXCHANGE

Flexner and associates [Flexner & Gellhorn (81), see Reynolds (198)] have found wide differences in the rates of transfer of given electrolytes across various types of placentas. Thus, in the ninth decile of gestation the transfer of Na is 0.026 mg per hour per gram of placenta in the so-called epitheliochorial placenta and 6 to 8 mg per hour per gram of placenta in the hemochorial placenta. Intermediate rates of transfer are found in the syndesmochorial and endotheliochorial placentas. Although it is believed by some that Grosser's classification of placental types has outlived its usefulness [cf Amoroso (6)], it is possible that the classification expresses a general tendency toward morphological organization and functional capability that is not entirely negated by dwelling on details of isolated microscopic fields either in the several types of placentas or in any one placenta. One may accept the fact that there are differences in morphology, but these are not sharply defined either within one placenta at various stages of pregnancy or

among many types of placentas. In this way, it becomes possible to account for the occurrence of fetal erythrocytes in the maternal blood and vice versa (see below).

VASCULARITY AND ACCOMMODATION OF THE PRODUCTS OF CONCEPTION

The adaptation of the vasculature of the nonpregnant uterus to the changes of gravidity is met in various ways in the several types of uteri: through growth and enlargement of the blood vessels [Orsini (164), Werbster (241), Schwarz & Hawker (218)] and by physical rearrangement of blood vessels as the uterus enlarges and changes the spatial orientation of the uterine blood vessels, especially as the uterus is finally stretched in the latter part of pregnancy. In all nonpregnant uteri numerous arteries are tortuous, coiled, or undulating [Ramsey (180)]. These tortuosities in the blood vessels permit their extension to accommodate in part the increase in size of the uterus. In sheep, one or two of the uterine arteries approach each cotyledon. The vessels divide into five or six trunks and pursue a tortuous course in the submucosa before dividing again and entering the cotyledon [Barcroft & Barron (19)]. The early pattern of these structures seems not to change during

FIG. 10 (facing page). Distribution of fetal arteries and veins to cotyledons of placenta of Père David's deer. Note that arteries and veins are of about equal size and number, indicating about equally rapid flows of blood in them. 1. Three injected cotyledons. Nearly natural size. 2. Section through middle of placentome. Masson stain. Natural size. 3. Drawing of three injected villi, removed from placentome. Central vessels of the villus and the intraepithelial capillary network are shown. 4. Section through fetal zone of placentome showing stem villus and to vessels. $\times 50$. Left and right, thin strands of maternal connective tissue from which epithelium is removed. [From Harrison & Hamilton (95). Courtesy Cambridge University Press.]

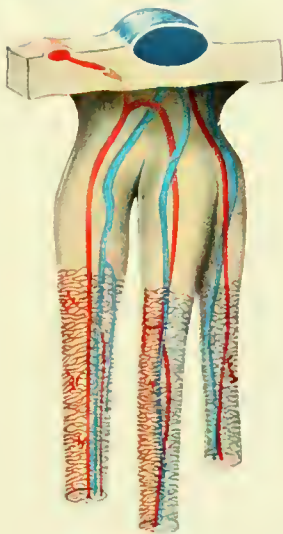
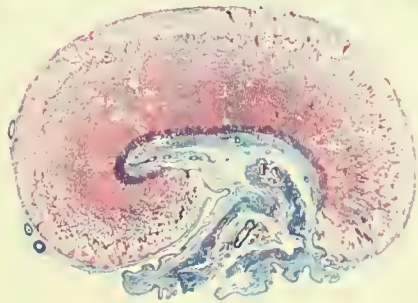
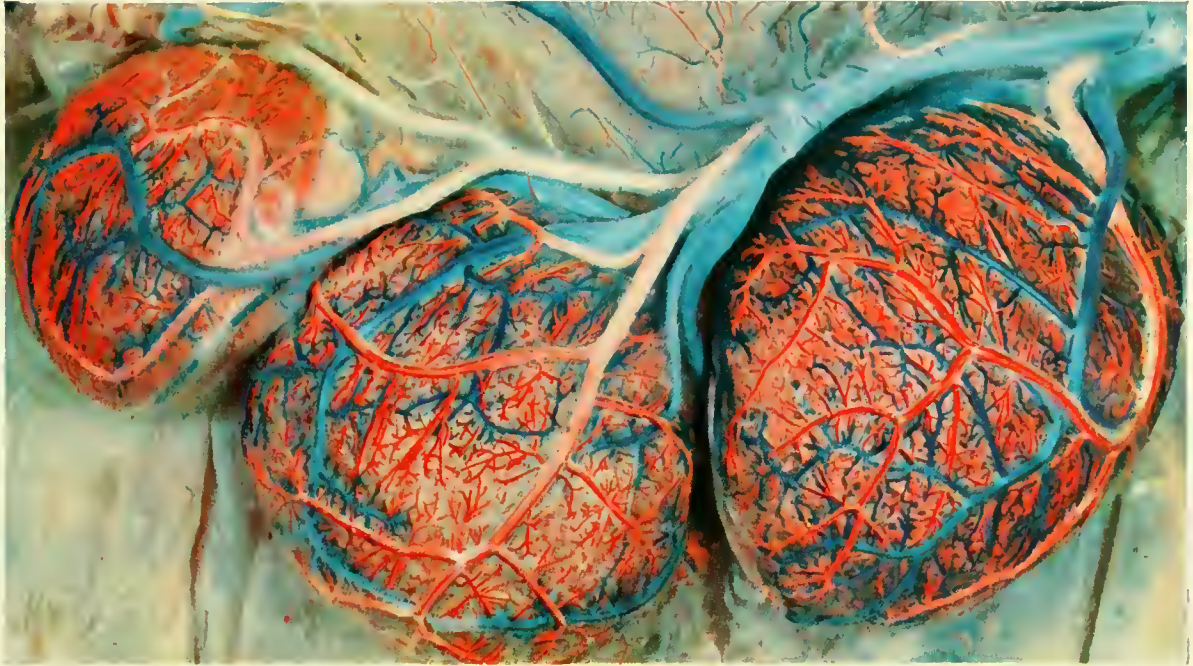


FIG. 10. See legend on facing page.

pregnancy except that the uterus is distended as pregnancy advances and increases steadily.

Harrison & Hamilton (95) have demonstrated especially well the relation of maternal and fetal blood vessels to each other in a deer. (See below for discussion of the fetal blood vessels in the hemochorial placenta.)

In the monkey, as the endometrium becomes thinner because the uterus is distended by the conceptus, the arteries become extended and the number of arterial connections with the intervillous spaces increases by development of smaller branches. Subsequently, the ends of adjacent vessels coalesce to form terminal dilations from which a single opening with a large accumulation of lining cells passes through the basal decidual plate into the maternal lake of blood [Ramsey (183)]. In the human, similar arrangements exist [Lundgren (137)]. Arterio-arterial shunts in the uterus exist among these vessels [Heckel & Tobin (100), Reynolds (199)]. As pregnancy advances, the number of arterial openings into the villous lake decreases substantially. Uterine blood vessels, along with all other tissues of the uterus, grow by hypertrophy and hyperplasia of their component parts during pregnancy [Reynolds (198)]. The cause of this is partly hormonal, partly the result of distention of the tissues. Hormones and distention interact to effect the growth response of the uterus during pregnancy (198).

For many reasons, therefore, the physiologist who would study blood flow would be well advised to appreciate the complexity of structural and functional factors involved in the uterus in different functional states.

The adaptation of the uterine vasculature to the uterus during pregnancy has been especially well studied in the rabbit [Reynolds (199)], which is typical of the uterus duplex and, with some modifications, to the uterus bicornis. A certain parallel exists also with changes that occur in pregnancy in the uterus simplex [Ramsey (187)].

In the rabbit, the vascular system of the uterus consists of large vascular channels which intercommunicate freely, both longitudinally along the mesometrial border of the uterus and circularly along the length of the uterus. This is well shown by Orsini (164) in the hamster. Of these large channels, the mesometrial arcuate vein is concerned primarily with draining the region of the uterus to which placental sites are attached. The lateral arcuate veins on each side of the uterus drain the larger part of the uterine wall. Each of these vascular beds is supported by the same incoming arteries and drained by the veins of the broad ligament. The implication of such an arrangement is clear. If, due to distention, the blood flow is reduced in one area (i.e., the peripheral vascular resistance increases), the flow of blood to the

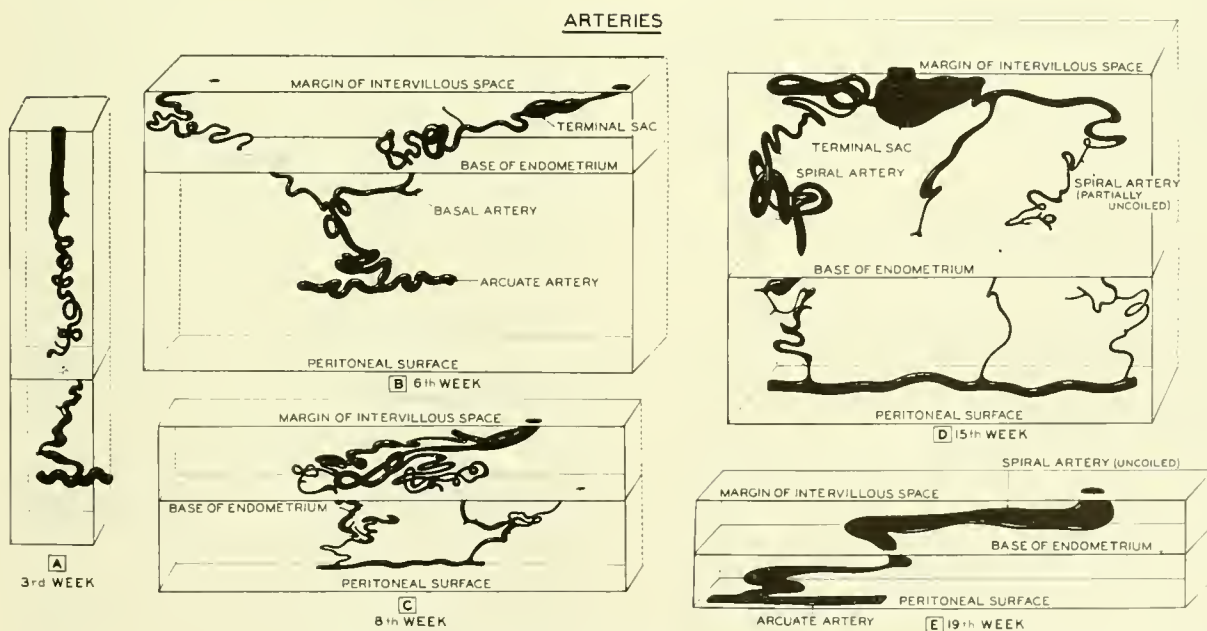


FIG. 11. Pattern of arterial supply to basal plate of the monkey placenta at different stages of pregnancy. [Permission of Ramsey (181).]

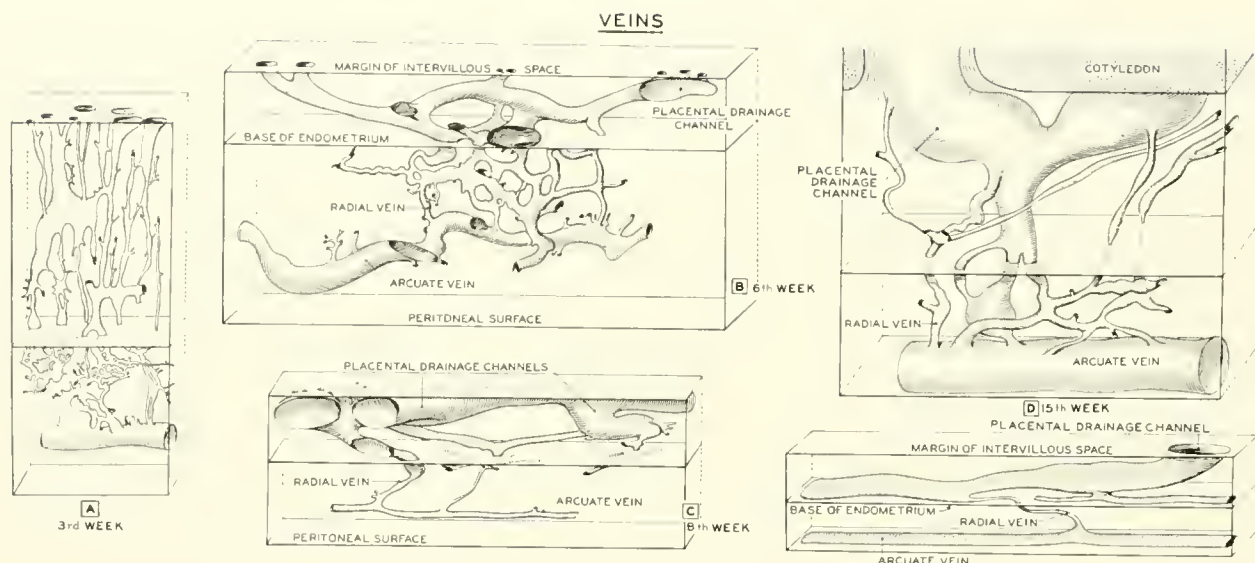


FIG. 12. Pattern of veins draining basal plate of placenta in the monkey at various stages of pregnancy. [Permission of Ramsey (181).]

other vascular bed increases so that it receives a larger portion of the incoming arterial blood to the uterus.

MENSTRUATION

The morphological and physiological mechanisms of menstruation have been the subject of considerable interest, particularly since precise knowledge of uterine rhythmic cycles was first established some forty years ago. Reviews on the subject in a modern context began to appear when Hartman (96) discussed the subject of intermenstrual bleeding. Bartelmez (23) gave us the first comprehensive review of the subject, however, and this was extended and revised in the light of later information by Reynolds (196), by Smith & Smith (222) and by Kaiser (124). Since that time, remarkably little attention has been directed to the problem.

In the uteri of certain but not all primates there are numerous coiled arterioles in the endometrium [Daron (62), Dalgaard (59), Kaiser (121), Bartelmez (26)] which are demonstrable in conventional tissue sections [Kaiser (121)]. These arterioles undergo increase in coiling throughout the menstrual cycle, reaching maximum development prior to menstruation [Daron (62), Kaiser (121)]. Van Wageningen (237) notes that it is vasoconstriction of these vessels [not coiling, as commonly supposed (61)] which causes ischemia. Then, due to hormonally induced changes within the tissues [Smith & Smith, (222)], there is loss of tissue fluid and thinning or regression of the

endometrium, and this results in congestion and stasis of blood in the coiled vessels [Markee (144)]. Subsequently, the superficial layers of the endometrium degenerate, slough off in an irregular but spreading manner as menstruation takes place. Sloughing begins when the endometrium is about one-half of the peak thickness prior to the end of the cycle. Bleeding is by capillary seepage, by reflux venous hemorrhage [Markee (144), Daron (63), Bartelmez (22)], and occasionally by brief arterial spurting of blood [Markee (144)]. Menstruation begins in localized areas and extends to others to involve the entire area [Strassman (228), Phelps (172)]. A role of arteriovenous shunts in the menstrual process is both alleged [Schlegel (216), Dalgaard (59)] and denied [Bartelmez (24)], but the evidence at hand seems to favor the former view [see Hertig & Rock (104)]. The physiological effect of coiling the arterioles of the uterus can hardly be different from that of coiling of vessels in the ovary and the testicle. Here, it lowers the blood pressure to the tissues beyond the coil [Reynolds (200), Waites & Moule (240)].

Since menstruation has been shown to be associated with local hemodynamic changes within the tissues concerned, some investigators have attempted to induce profound hemodynamic disturbances with a view to causing uterine bleeding. This has been done [Van Wageningen & Zuckerman (238), Markee *et al.* (145)] but not invariably so [Emmel *et al.* (69)]. The effect of cord transection depends upon a proper effective estrogen level.

The critical factors in determining what manipula-

tions or hormone treatments will produce menstruation are related to the nature of the vasculature of the endometrium. This is affected by the previous menstrual history of the organism since each cycle brings about some residual changes through growth of the vascular tree which persist to affect the next cyclic bleeding [Phelps (173)].

In addition to the idea that changes in the uterine vasculature affect and modify the menstrual process, Smith (220) and Smith & Smith (221) hold to the view that a toxic substance is produced within the endometrium, secondary to the premenstrual ischemia, and that this toxin leads to the breakdown of the tissues and the ensuing menstrual discharge.

Prostigmin, a vasodilating substance, has been shown to cause uterine bleeding in nonpregnant women [Soskin *et al.* (223)], but not in pregnant women. Kaiser (123) failed to observe a similar response in the rhesus monkey. This drug also failed to affect estrogen-induced hyperemia in endometrial ocular transplants in the rabbit [Kaiser (125)].

In the nonpregnant endometrium of both rabbits and monkeys, there are rhythmic constrictions and dilations of the minute vessels which are independent of the nervous system [Markee (142, 144)]. Under the influence of estrogen there is persistent hyperemia of the endometrium [Pompen (176), Markee (143)]. The significance of the rhythmic vascular changes, both as to cause and as to function, are unknown. They are, apparently, unique to endometrial vessels, although estrogens do have profound effects on somatic minute vessels [see Reynolds (198)], especially integumentary, in rabbits and humans [Reynolds & Foster (206, 208)], and in the nasal mucosa [MacKenzie (139)], as well. The retinal circulation is also modified in women, manifesting itself by scotomata that change in position with change in posture [Evans (72)]; this is marked in the last half of the menstrual cycle.

Of importance to the vascular architecture in the endometrium is the seldom emphasized fact that the tissue in which these structures lie is loose and spongy. The vascular elements are developed out of all proportion to the immediate vascular needs of the tissue [Reynolds (196)]. It is clear that the vascular arrangement is adapted to the future needs of supplying and invading the implanting trophoblast [Hasner (98), Bartelmez (25)]. This instance is not unique in developmental biology where nature has repeatedly contrived to anticipate future needs by prior organization of mechanisms. When a trophoblast fails to develop, the complex vascular structure of the endometrium breaks down since it cannot be maintained

in the face of the requirements of cyclic endocrine activity in which ovulation is the focal point of the pattern. This endometrial cycle occurs, even though ovulation may not occur. Moreover, most uteri, even including those of some primates [Kaiser (120), Hamlett (93), Goodman & Wislocki (85)], do not manifest endometrial sloughing even though they exhibit microscopic bleeding; instead, the endometrial vessels undergo an ebb and flow of cyclic growth and regression unaccompanied by profound menstrual process. In either event, the local vasculature changes cyclically. In some species, such as rats, hamsters, and guinea pigs, the cyclic occurrence of localized areas of hyperemia within the uterus is evident (see below).

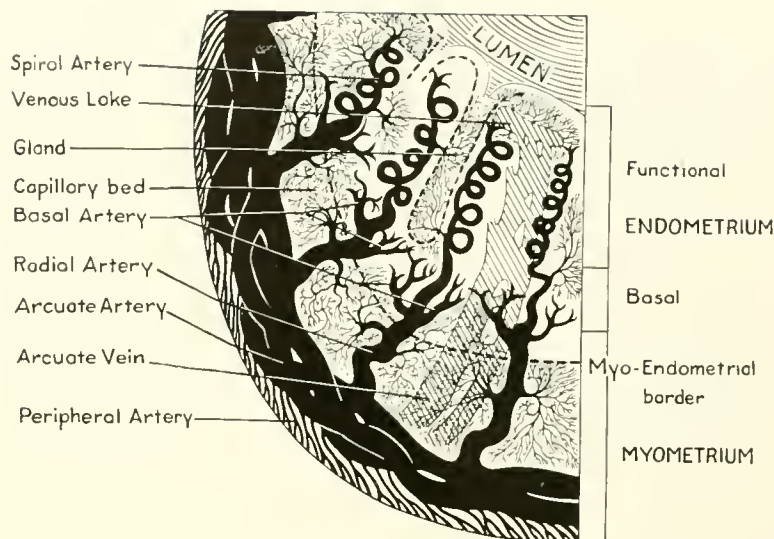
HORMONES AND THE UTERINE VASCULATURE

The endometrial hyperemia, indeed the entire uterine hyperemia, that occurs periodically has a metabolic basis under endocrine control. Estrogen augments the amount of acetylcholine found in the uterus [Reynolds (193, 203)] and in the nasal mucosa as well [Reynolds & Foster (207)]. However, it was later found that it is the change in cholinesterase which accounts for this [Everett & Sawyer (73), Herschberg (103)]. It is also reported that the hyperemia is associated with alterations in the amount of histamine or histamine-like substances in the uterus [Kaiser (122)]. It appears that one can only say that there is a change in vasoreactive tissue constituents under the influence of estrogen and it is probable that more than one substance is involved.

UTERINE CONTRACTION AND BLOOD FLOW

The circulation in the uterus, like that in all muscular viscera, functions in the face of contraction and relaxation of the muscular components of the organ. It must serve with great efficiency as the uterus undergoes great change in size and shape during pregnancy. The consequences of contractions, growth, and distention upon blood flow in the uterus require consideration. Certainly, clamping of the blood supply to the uterus elicits uterine contractions, as Rorhrig showed many years ago [see Reynolds (198)]. In this respect, myometrium is no different from intestine or other smooth muscle. More delicate, however, is the observation that low arterial blood pressure is associated with an increase in frequency and amplitude of uterine contractions [Kunisima (132), Robson

FIG. 13. Schematic representation of arterial supply to portions of uterus simplex (monkey, human). [From Reynolds (196).]



& Schild (212)], while an induced higher blood pressure has an opposite effect. Ahlquist & Woodbury (2) found in cats that when intrauterine pressure reaches 60 to 70 mm Hg, uterine blood flow virtually ceases. This is reminiscent of the report by Moir (156) that when intrauterine pressure exceeds arterial blood pressure, a woman feels ischemic uterine pain. It may be that myometrial smooth muscle acts in concert with that of the uterine blood vessels themselves. In myometrial studies, adrenaline and noradrenaline cause decreased uterine blood flow in rabbits and guinea pigs, associated with uterine contractions [Dornhorst & Young (67)], but an action on uterine blood vessels was not eliminated. The consequence of strong uterine contractions on the systemic circulation are shown by the fact that undulatory changes in arterial blood pressure occur as the postpartum uterus contracts [Franklin (82)].

For many years, speculation existed concerning the effect of uterine contractions on the flow of blood in the placenta of the human. Two possibilities existed: *a*) that the contraction squeezes blood out of the placenta as water may be squeezed out of a sponge [Kermauner (128), Grosser (89, 90)], and *b*) that as the intervillous space pressure builds up, veins are at first occluded, then pressure increases in the intervillous space as it increases in the amniotic cavity [Keiffer (127), Wagner (239), Pryztowski (179)]. Meanwhile, blood remains in the placenta to meet the needs of maternal-fetal exchange during uterine contraction. There is now no doubt that the second view is correct. This was suggested indirectly by the work of Woodbury *et al.* (250) and shown clearly by Woodbury *et al.* (251), Alvarez & Caldeyro

Barcia (3), Caldeyro Barcia (50), and by Pryztowski (179) in women and by Ramsey *et al.* (188) in monkeys.

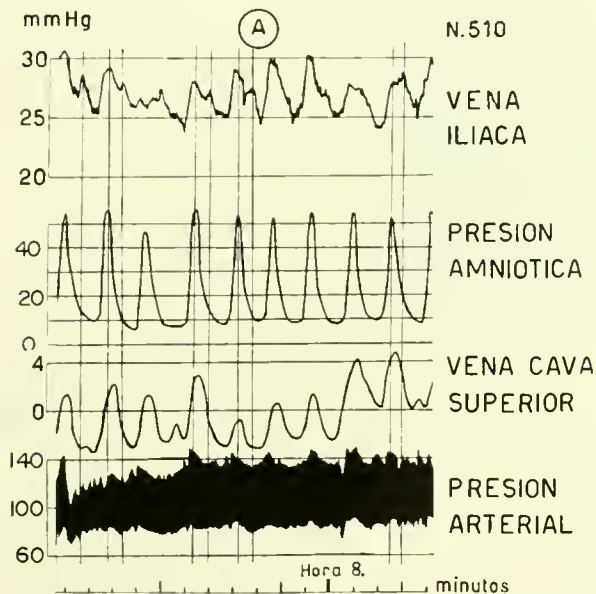
BODY POSTURE AND UTERINE CONTRACTILITY

Perhaps the most telling observation about the effect of uterine circulation on uterine contractions is the observation made in women that a change in posture modifies the quality of uterine contractility. When a woman in late pregnancy or in labor lies on her back, uterine contractions of a given frequency and intensity (i.e., change of intrauterine pressure) are seen [Williams (246), Caldeyro Barcia *et al.* (51)]. When she assumes a semireclining posture, or turns on her side, the contractions become slower and more intense. With a view to studying the role of compression of the inferior vena cava in the recumbent position, pressures were recorded simultaneously in a woman in the lower and upper parts of the vena cava [Caldeyro Barcia *et al.* (51)]. The weight of the gravid uterus on the retroperitoneal surface caused a disassociation of the venous pulse pressures in the two parts of the vein; with the woman on her side, the venous pulse waves became synchronous, and the quality of uterine contractions changed.

ESTROGEN AND UTERINE BLOOD VESSELS

Another indication of the relation between uterine contractility and uterine blood flow lies in the observation that, following estrogen withdrawal, the

EMBARAZO NORMAL DE TERMINO
PARTO INDUCIDO PITOCIN I/V $\frac{1}{200}$ U. por min
DECUBITO DORSAL



EMBARAZO NORMAL DE TERMINO
PARTO INDUCIDO PITOCIN I/V $\frac{1}{200}$ U. por min
DECUBITO LATERAL DERECHO

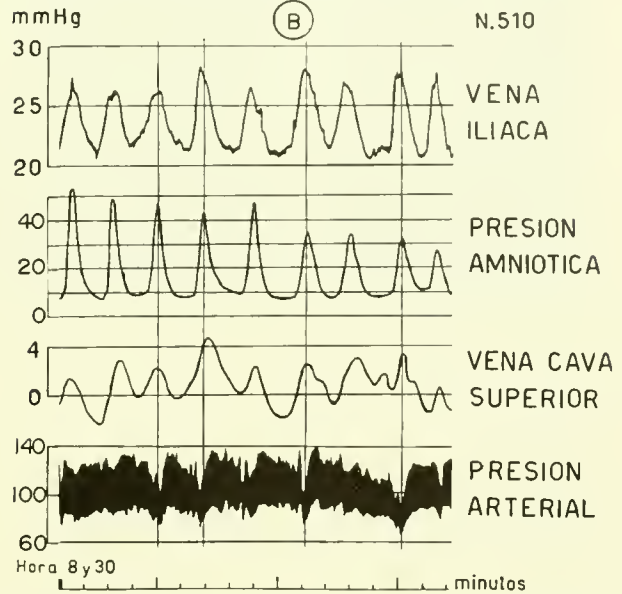


FIG. 14. Effect of body position on pressure in the iliac vein, superior vena cava during late pregnancy and arterial blood pressure. A: on back. Note bimodal pressure peaks. B: on side. Note single simultaneous pressure peaks in upper and lower vena cava, synchronous with acme of uterine contractions and lower systolic blood pressure. [Permission of Caldeyro Barcia *et al.* (51).]

uterus becomes less hyperemic and gradually loses its contractility [Reynolds (191)]. Within an hour after estrogen is injected there is an intense hyperemia [Markee (142), Pompen (176)]. Twelve or more hours later the myometrium becomes active [Reynolds (190)]. Beginning activity depends upon synthesis of actomyosin in the uterus [Csapo (57)]; this is related to a rise of aerobic metabolism of the uterus [MacLeod & Reynolds (140)]. There seems to be an assumption that this is solely in the smooth muscle of the myometrium. It is possible, however, that smooth muscle in the uterine blood vessels is equally estrogen-dependent; this has not been investigated. Certainly, with prolonged estrogen withdrawal the blood vessels of certain parts of the uterine vasculature show a reversible hyaline degeneration [Okkels & Engle (163), Kahn & Laipply (119)]. All parts of the vasculature are not equally affected. The very first effect of estrogen on the uterine vasculature is to cause capillary dilation [Pompen (176), Fagin & Reynolds (74)]. Its role in affecting the larger vessels seems to have attracted very little attention although stilbestrol raises the arterial pressure in female but not in male rats [Hill (106)].

When estrogen given to rabbits is combined with

progesterone in relatively massive doses, profound hyperemia of the uterus occurs [Gillman (84)]. Extensive sloughing of the endometrium results. Estrogen alone increases capillary permeability [Hechter *et al.* (99)] which is associated during the first 6 hours with an increase in the relative wet weight of the uterus of ovariectomized rats. Later the relative dry weight increases progressively to a maximum about 24 hours after the injection [Astwood (13)].

The mechanism of the estrogen-induced hyperemia is indicated by the fact that estrogen increases the acetylcholine-content of rabbit uteri within 1 hour [Reynolds (193)], and its concentration in the uterus changes during pregnancy [Reynolds & Foster (205)]. One group of workers failed to confirm the response in rabbits [Emmens *et al.* (70)] for unknown reasons. Even so, estrogen seems to affect the acetylcholine of the uterus by altering its cholinesterase content [Herschberg (103), Sawyer & Everett (215), Everett & Sawyer (73)]. Pompen (176), it will be recalled, found that the uterus *in situ* does not become hyperemic under estrogen if atropine is administered. Kaiser (125), however, failed to observe this if the endometrium is transplanted, and without an innervation.

Sturgis (229) found that anything which alters uterine blood flow in the monkey may affect the rate of fluid formation in the uterine lumen (glandular secretion?). This lead has never been followed up, or studied in relation to endometrial physiology or cytology.

In the absence of large amounts of estrogen, but not in ovariectomized rabbits or guinea pigs, the capillaries of the endometrium exhibit a rather rapid rhythmic blanching and blushing [Markee (141, 142)]. This phenomenon is unrelated to myometrial activity. Since capillaries lack contractile elements, it must be, therefore, a manifestation of arteriolar activity.

UTERINE INNERVATION

There is a rich sympathetic innervation to the uterus [Reynolds (198), Krantz (130)]. The parasympathetic innervation is limited, so far as is known, to the region of the cervix. Despite the nerve supply, a uterus which is denervated by transplantation to the ventral peritoneal wall possesses all the normal nongravid reactivity of the uterus in situ [Reynolds & Kaminester (209)]. This is not to say that the innervation is without effect upon the vasculature [Reynolds & Kaminester (210)]. Rather, the hormones are independent of the innervation in their action on the uterus. Certainly, fright causes vasoconstriction, but it is possible that this is a hormonal effect of blood-borne epinephrine [Markee (142)]. Few data exist which suggest, much less show, what the normal role of the vasomotor innervation to the uterus is. The existence of vasomotor nerves, however, as entities separate from the nerves which supply the myometrial smooth muscle has been amply shown [Medowar (149)]. Vasodilator fibers may exist since cholinergic sympathetic fibers to the uterus seem to have been demonstrated, as well as adrenergic ones [Burn (46)]. Moreover, atropine has been seen to reduce the hyperemic effect of estrogen on the uterus in situ [Pompen (176)] but not in denervated endometrial transplants in the eye [Kaiser (125)].

PREGNANCY AND THE UTERINE CIRCULATION

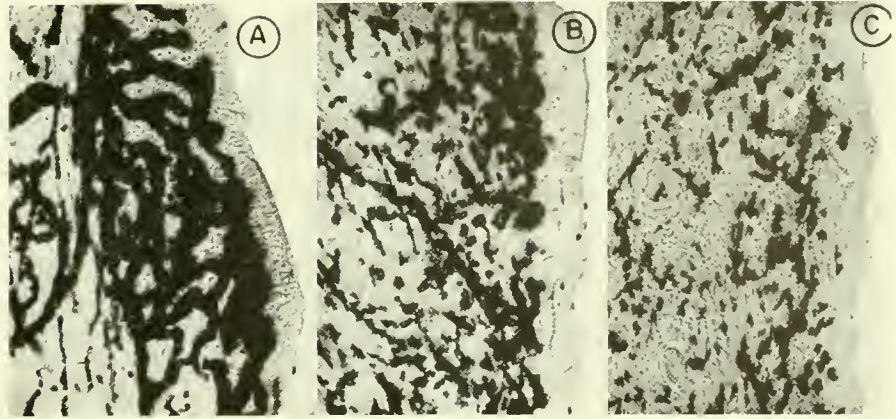
Pregnancy imposes an array of special requirements upon the uterine circulation. These are, as mentioned above, responses to growth of the conceptus and spatial adjustments that are of great magnitude.

At the outset of pregnancy, the uterine hyperemia of estrus gives way to a quality in the circulation in the uterus prior to implantation and for a time after which renders the uterus bluish in appearance as if the circulation were turgid. This is seen with the uterus in situ [Barcroft & Rothschild (21)] and in ocular grafts [Neumann (160)]. Aside from the generalized uterine hyperemia referred to above, localized hyperemia, more marked in some parts of the endometrium than in others, has long been known and suspected to be related to implantation. This was reported in the human by His (108), Hitschmann & Adler (109), Strahl & Beneke (227), Delporte (65), Teacher (231), Falkiner & Fleming (76), and Wilkin (242). More refined examination of this in controlled experiments on animals awaited the work of Bacsich & Wyburn (15-17) in the guinea pig and more recently in the rat [Williams (246), Holmes & Davis (112)] and hamster [Orsini (164)]. Perhaps the most remarkable instance of localized implantation is found in the South African shrew, *Elephantulus myurus jamesoni*, which has a uterus duplex. This species sheds dozens of ova at each ovulation; all become fertilized but only two become implanted, one in each uterus in a region of remarkable vascular development [van der Horst & Gillman (115)].

The meaning of the above relationships is being studied by Böving (36, 37). Implantation occurs in the vicinity of a single capillary loop lying beneath the endometrial epithelium. Attachment (in the rabbit) takes place when the abembryonic pole of the blastocyst develops a sticky substance that is lacking over the embryonic pole. This substance is related to a gradient of alkalinity occurring within the blastocyst and is associated with the differential in production of metabolites between the embryonic pole and the abembryonic pole of the blastocyst. The concept is that the blood flowing through the capillary loop removes CO₂ about as fast as it is produced, leaving behind on the surface of the blastocyst a calcium-protein residue that is sticky. Carbonic anhydrase is present in high concentration in the endometrium [Lutwak-Mann & Laser (138)]. The epithelium of the endometrium breaks down when attachment occurs [Böving (37)]. In intraocular transplants in rats, trophoblast causes a breakdown of capillaries [Grobstein (86)] as it does in the endometrium [Mossman (158)].

From this time until the period of uterine conversion (see above), when the pregnant uterus changes from spheroidal to an elongating form, the uterine vasculature undergoes enlargement and its blood

FIG. 15. Local vasodilating action of estrogen in endometrium of guinea pig. *A*, anti-mesometrial; *B*, lateral; *C*, mesometrial. [From Bacsich & Wyburn (15).]



volume increases [Orsini (164), Reynolds (199)] coinciding with the period of most rapid uterine enlargement. From this time until near term, there is a period of diminished blood in the vascular bed until term, when a period of partial hemostasis supervenes [Barcroft & Rothschild (21), Reynolds (192, 196)]. These changes are supported by studies of bits of transplanted endometrium to the anterior chamber of the eye [Neumann (160), Krichesky (131)].

When the uterus is in situ, the blood vessels over the conceptus give evidence of hypertrophy and the tortuous course of the uterine arteries progressively changes as they straighten out [Reynolds (199)]. This is associated with local distention of the tissues by the conceptus. Distention is a factor in uterine hypertrophy [Reynolds (198)]. The veins, showing no initial tortuosities, can only adapt by growth, stretching, and proliferation. In the uterus duplex, the vessels in the interconceptus sites show no such changes. Only as the spheroidal conceptuses enlarge and encroach upon the interconceptus sites do the blood vessels there become involved in extension and stretching. These processes continue until a phase of maximum spheroidal size is attained. At this time, vessels that have been crowded from about each conceptus toward the interconceptus sites lie close together; those that lie around a conceptus are stretched and, in any one area, sparse. Within a very short period of time (in the order of hours), the rapidly enlarging conceptus breaks out of its spheroidal shape as it pushes along the uterine lumen into less distended regions of the uterus. When this happens, the vessels of the interconceptus region slip with the tissues in which they lie over the conceptus, much as a stocking is slipped up a leg. After this, the enlargement of the conceptus is solely by elongation, without further increase in diameter. This elongation con-

tinues until shortly before term, at which time a second limit of distention is reached and stress is placed upon the circulation for a second time. In any event, at a time when fetal growth and demands upon the circulation are great, the uterine blood vessels merely become rearranged so as to minimize the hemodynamic work of the maternal circulatory system in supplying the uterus and its contents.

How is blood flow in the uterus modified as these changes take place? By measuring local circulation times [Reynolds (194, 199)], it has been found that as the spheroidal conceptus enlarges there is a progressive decline in the circulation rate until the time of conversion. Just prior to conversion, there is a profound hemostasis in the tissues about a conceptus. Upon release of tissue tension by the act of conversion, a sudden increase in local circulation rate takes place, approaching that observed at the start of pregnancy. As gestation nears its end, there is a second decline in blood flow concomitant with the longitudinal stretching of the uterus prior to parturition.

The flow characteristics described above relate to the flow in the maternal vessels of the uterine wall, not to the other part of the uterine circulation, which goes to the placenta. Here, there must be adequate flow at all times, otherwise the fetus will be endangered. No objective study has been made of the manner by which this is accomplished, but it has been speculated that the governing factor is the changing shape of the pregnant uterus combined with tension in the uterine tissues [Reynolds (195)]. Blood flow is reduced to the tissues of the uterus which are most concerned with change of shape in order to accommodate products of conception, and at the same time blood is directed toward the placenta, since both parts of the system are supplied by the same arteries at the border of the mesometrium. This is to say that as the peripheral vascular resistance increases in one

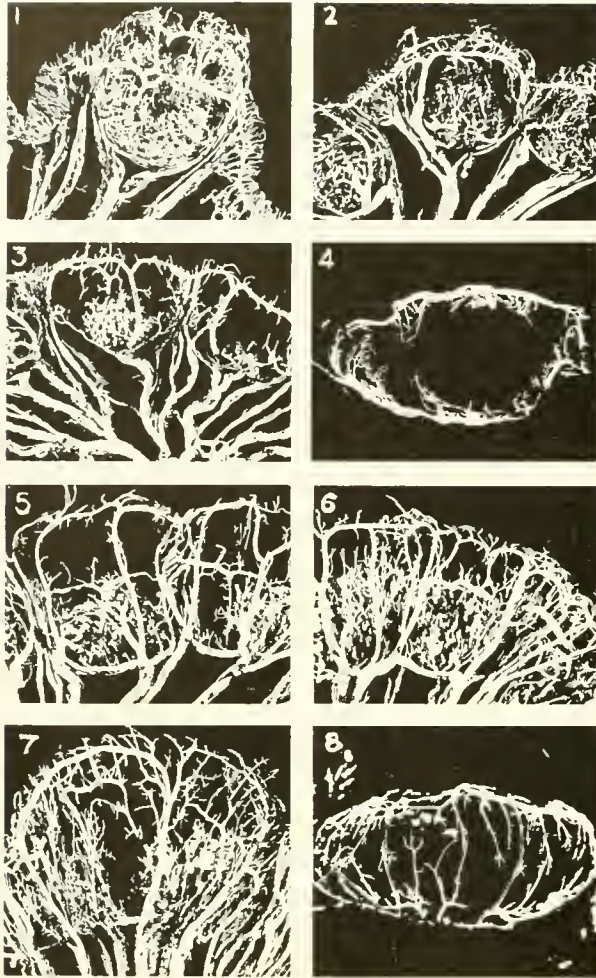


FIG. 16. Injected arteries of rabbit uterus on 12th day (1), 16th (2), 20th (3, side view; 4, antimesometrial view), 22nd (5 and 6) 24th (7 and 8) of gestation. Note diminishing injectibility of blood vessels as uterus reaches maximum spheroidal distention on day 22. [From Reynolds (199).]

part of a common vascular bed, flow to the other area is favored, since the peripheral vascular resistance there, while unchanged, is relatively less than in the first area. Study of the vascular rearrangements in the pregnant monkey uterus show that a comparable pattern of vascular arrangements occur in the uterus simplex [Gillespie *et al.* (83), Ramsey (187)].

Physiologists have long been concerned with uterine blood flow. Barcroft and his associates measured total uterus blood volumes and blood flows in the uterus of the rabbit throughout pregnancy [Barcroft *et al.* (20), Barcroft & Rothschild (21)]. It was found that both increase but in dissimilar patterns. From a content of about 2 ml at the outset of pregnancy in the rabbit, the uterine blood volume increases to more

than 30 ml by day 27, whereupon it declines 50 per cent in the next 3 days. The blood flow increases to two peaks of 30 ml per min on the 20th and 27th days (gestation 31 days), with the decline in total blood flow to less than 20 ml on day 24. It will be seen that the local deprivation of blood in uterine tissues described in the regional studies above were reflected also in the total blood flow [Reynolds (192)]. Page (167), using an indirect method of reasoning based on facts, shows that in the ninth month of pregnancy in women there is a decline of nearly one-half in uterine blood flow.

The turnover of blood in the pregnant rabbit uterus based on the flow divided by the volume, shows a progressive increase from about 60 per cent turnover on the 12th day of pregnancy to 175 per cent turnover on day 20 with a sustained 75 to 85 per cent turnover after uterine conversion. Comparing the turnover characteristics with the factors of uterine growth and distention, one sees how affected by or related to these factors the uterine circulation is [Reynolds (192)].

Recent studies have been directed toward the measurement of total uterine blood flow in sheep and humans. These have been of three types. In the sheep and humans, arterial and venous blood sampling and application of the Fick principle have been used. In

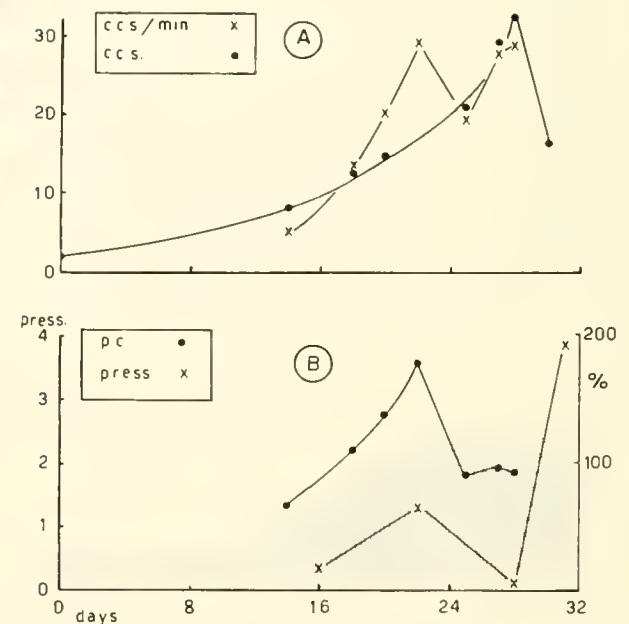


FIG. 17. A: blood flow (x) and blood volume (●) in rabbit uterus during pregnancy. B: percentage turnover of blood (●) related to uterine growth (stippled area) and intrauterine pressure (x). [From Reynolds (192), based in part on Barcroft *et al.* (20).]

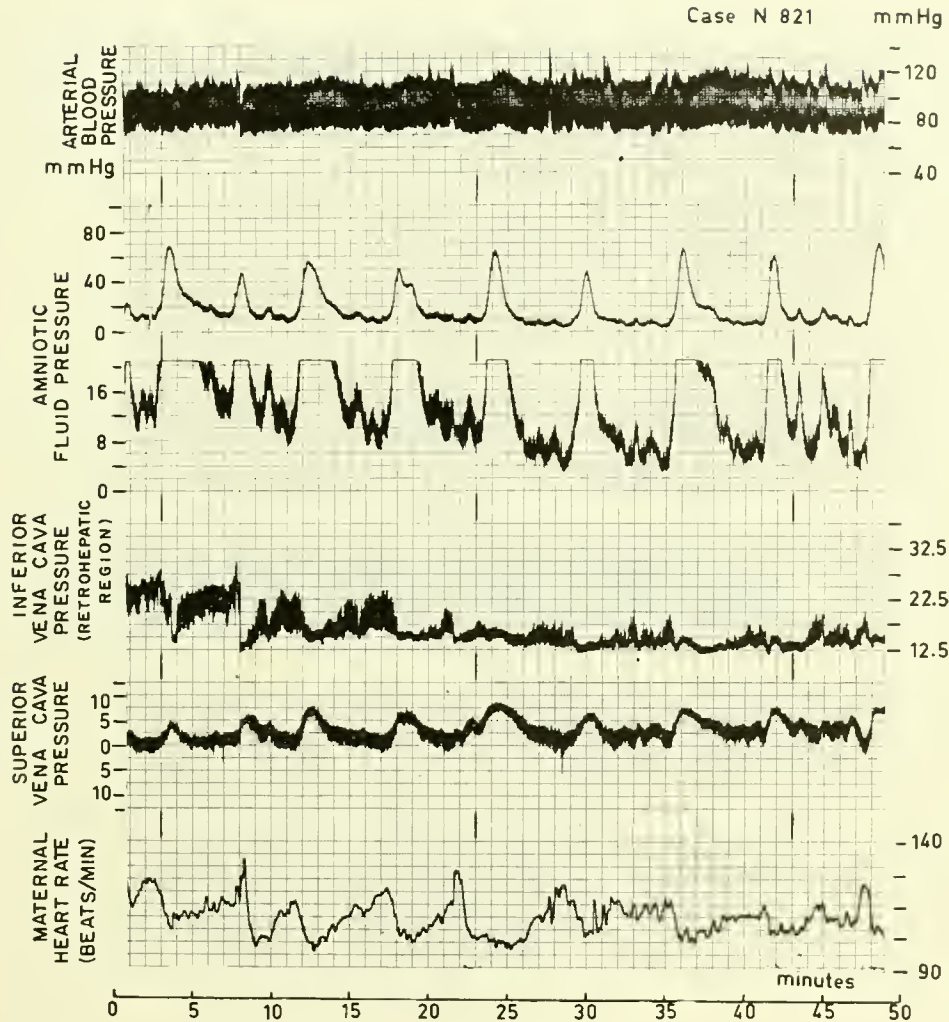


FIG. 18. Effect of uterine contraction in women on maternal circulation. Uterine pressure is shown on two sensitivity scales (0-100 mm Hg; 0-20 mm Hg to show effect of tonus in latter record on vena cava pressures, superior vena cava, and retrohepatic). Note decrease in inferior caval pressure as uterus contracts when tonus is high but not when tonus is low. Note bradycardia during contraction. (Permission of Bieniarz *et al.*, XX1 Int. Cong. Physiol. Sciences, Buenos Aires, Aug. 1959.)

the ewe, continuous monitoring of uterine blood flow in a uterine artery has been done with an electromagnetic flow meter. The third method involved injection of radioactive sodium into the intervillous spaces and measuring the disappearance rate.

Metcalf *et al.* (154) found by use of a modified Fick principle (142) that the blood flow to the non-gravid uterus in sheep and goats is 25 ml per min. Slightly more than half way through pregnancy on the 80th day, the flow increases to 200 ml per min. At term, flow is more than 1 liter per min, a substantial increase in blood flow for an organ. The surface area of the fetal portion of the human placenta,

it may be noted parenthetically, is estimated to be about 15 m² [Christoffersen (53)]; the increase in placental villous surface area throughout pregnancy is described by Wilkin & Bursztein (245).

Metcalf *et al.* (153) have related the increase in blood flow as observed by them and others to the fetal demand, in the rabbit, human, and ungulate (sheep, goat). The relations are summarized as follows:

| | Rabbit | Human | Ungulate |
|----------------------------------------------------------|--------|-------|----------|
| Uterine blood flow per kilogram fetal weight (ml/kg/min) | 125 | 156 | 283 |

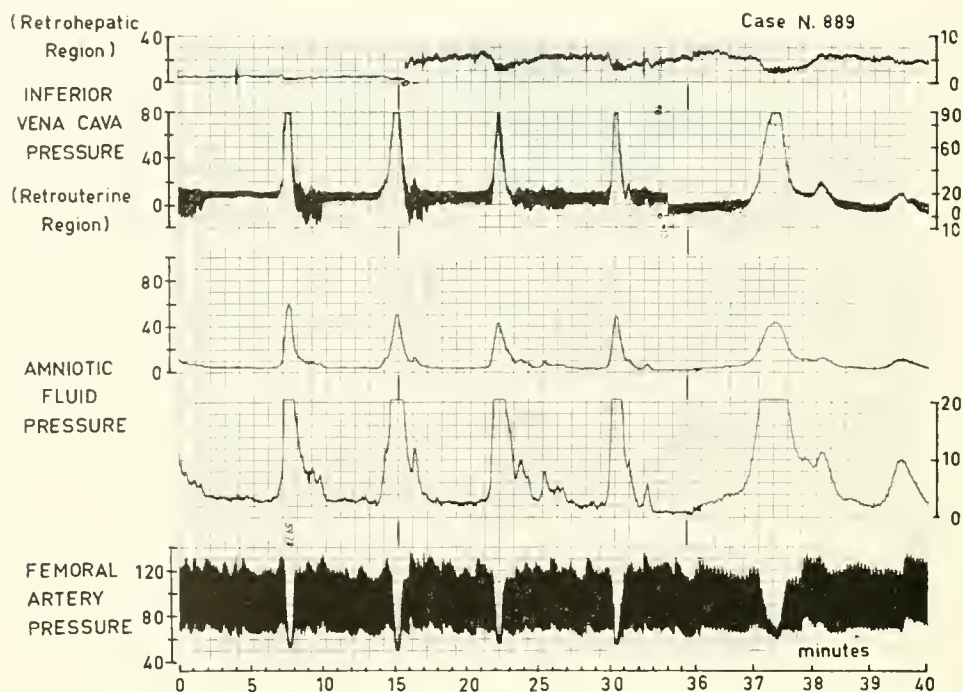


FIG. 19. Blocking of inferior (retrouterine) vena cava with strong uterine contraction. Note fall of arterial blood pressure as venous pressure rises. [Permission of Caldeyro Barcia *et al.* (51). See fig. 14.]

The above differences in maternal hemodynamic work are not related to the oxygen utilization of the fetus, as shown by the same authors:

| | Rabbit | Human | Ungulate |
|------------------------------------------------------------------|--------|-------|----------|
| Uterine oxygen consumption per kilogram fetal weight (ml/kg/min) | 8.3 | 7.4 | 8.9 |

The syndesimochorial placenta in terms of uterine work to supply a given weight of placenta appears to be far less efficient than the hemochorial type of placenta.

On admittedly less sure grounds, observations on human uteri have been made. Techniques of sampling, numbers of subjects, assumptions regarding uterine weights and other uncertainties all contribute to the interpretation of the data, and a number of workers have entered into this uncertain field. These reports are discussed by Metcalfe *et al.* (152). In their series, 13 single fetus pregnancies were studied. They found the blood flow to be of the order of 500 ml per min and the O₂ consumption of the uterus and its contents, 25 ml per min. In one twin pregnancy, both values were about doubled. It appears that the fetal load, or drain upon the uterus, may be a key

factor in determining how much blood flows to the uterus.² This is shown by the following data:

| | Single | Twin |
|-------------------------|--------|------|
| Uterine blood flow | 460 | 1150 |
| Uterine O ₂ | 25 | 48 |
| Uterine CO ₂ | 20 | 47 |
| Uterine RQ | 0.80 | 0.98 |

If this is for nonidentical twin pregnancies [not stated by Metcalfe *et al.* (153)], the result is understandable: there are two placentas to be supplied. If there were but one placenta, the results with respect to blood flow are less clear. Romney *et al.* (213) have added data in the human also.

With respect to the increase in uterine blood flow, Ramsey *et al.* (188) have pointed out, it is about half as great as the increase in maternal renal blood flow during pregnancy.

The problem of the utero-placental circulation as a

² Since this review was written, an important paper (H. Wulf. Der Gasaustausch in der reifen Plazenta des Menschen. *Z. Geburtshilfe u. Gynäkol.* 152: 117-134, 1962) with extensive literature review on gas exchange in the placenta has been published. While dealing mainly with gas exchange, it discusses the causes (including anatomical and physiological) of utero-umbilical oxygen and carbon dioxide tension gradients.

physiological burden on the circulation led Burwell (47-49) to regard it as an arteriovenous shunt. The blood-volume increase of the human uterus that occurs is reported by Caton *et al.* (52). The effect on the maternal heart rate, cardiac output, and blood volume are comparable to the effect of a major arteriovenous shunt in the cardiovascular system. In the latter part of pregnancy increases are seen in resting heart rate, cardiac output, circulation rate and blood volume [Hamilton (91), Palmer & Walker (169)]. In the last few weeks of pregnancy there begins to be a

decline in each of these as maternal oxygen consumption increases. The cause of these declines is not known, but one is reminded of the profound uterine ischemia seen in rabbits (*vide supra*) toward the end of pregnancy. The concept of the gravid uterus acting as an A-V shunt was first set forth in 1938 [Burwell (49)] and supported by the later studies cited above. The most recent summary is by Burwell (47). The circulatory load as a pathophysiological mechanism upon the circulation after birth when the A-V shunt is removed has drawn the attention of Schwarz (217) and the ischemia of the parturient uterus noted by Thoma (234).

Assali *et al.* (7, 8) were the first investigators to catheterize the uterine vein in women for the purpose of withdrawing blood samples that could be employed, when combined with simultaneous arterial samples, to use the Fick principle (nitrous oxide) in estimating uterine blood flow. Studying women in normal pregnancy, Assali *et al.* (9) found that the flow was 15 ml per 100 g of tissue per min. This value, approximating 150 ml per min, is surely low (see above). However, with the same method, they observed a decrease to 9 ml per 100 g of tissue per min in the first 24-hour postpartum period. Before commencing these studies, Assali (7) reviewed and criticized methods used previously.

A new departure in measurement of uterine blood flow was reported by Assali *et al.* (10) who monitored blood flow in a uterine artery of the pregnant ewe with an electromagnetic flowmeter during spontaneous and induced labor. Uterine contractions, spontaneous or induced, were accompanied by a significant decrease in blood flow which was more or less proportional to the strength of the contraction. During

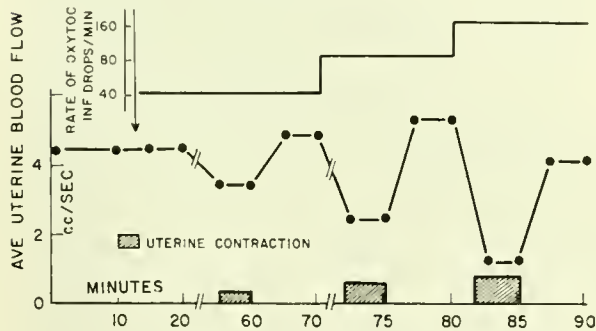


FIG. 20. Average uterine blood flow at term in uterus of ewe. The time scale does not refer to the duration of uterine contractions or to the duration of the decrease in flow. Although recordings were taken continuously, for the reason of space economy only one single contraction, with two blood flow readings, is given for each rate of oxytocin infusion. In early labor, uterine contractions occurred every 8-10 min and lasted for about 20-25 sec. Each contraction was accompanied by a decrease in flow. When the rate of oxytocin was doubled, contractions occurred every 4-5 min and lasted for 35-40 sec, and the flow was more reduced. With a further increase in the infusion rate, the contractions lasted for 45-60 sec and the reduction in flow was more marked. Note the rebound in flow during uterine relaxation. [Assali *et al.* (10).]

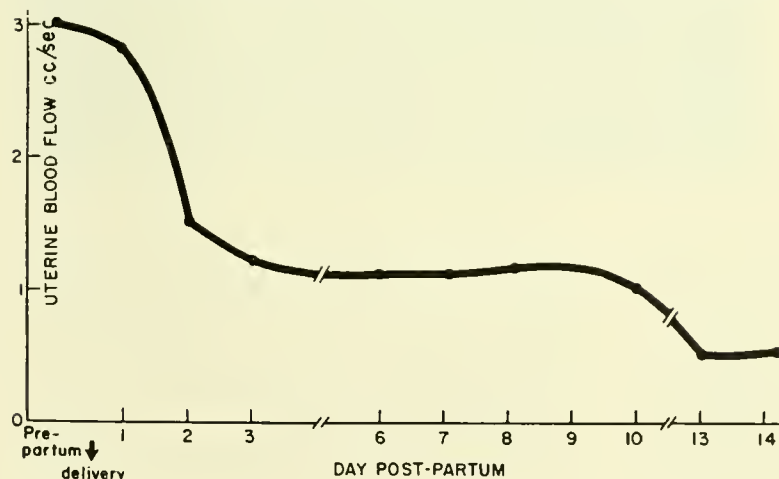


FIG. 21. Average uterine blood flow obtained during the puerperium in the ewe. Delivery of the placenta occurred between day 1 and day 2. Note the precipitous fall in flow which occurred after the expulsion of the placenta. The progressive decrease during the postpartum period coincided with uterine involution. [Assali *et al.* (10).]

FIG. 22. Identical pressures in amniotic fluid and intervillous space of placenta in the monkey with the uterus contracted or relaxed. [Permission of Ramsey *et al.* (188).]

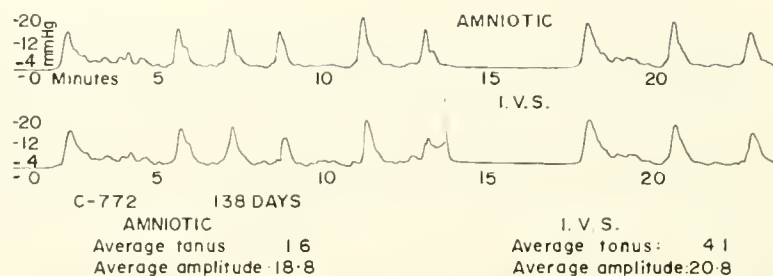


FIG. 23. Failure of India ink to reach a sinus structure at margin of monkey placenta. [Permission of Ramsey (185).]



FIG. 24. Injected lymphatics in uterus of a nearly mature rhesus monkey. Note paucity in superficial endometrium. (From Wislocki & Dempsey. *Anat. Record* 75: 341, 1939.)



uterine relaxation, reactive hyperemia set in. After labor, there was a precipitous fall in uterine blood flow which declined gradually with subsequent uterine involution.

The action of oxytocic, vasopressor, and vaso-depressor drugs on postpartum uterine blood flow was studied by the same method [Assali *et al.* (11)]. Both natural and synthetic oxytocics in large doses

cause an initial rise, followed by a marked decline in uterine artery blood flow. Epinephrine produces no significant change in uterine blood flow, although norepinephrine increases the diastolic pressure and mean blood flow. Apresoline (a sympatholytic agent) increases blood flow substantially.

In a study of uterine blood flow and uterine metabolism in women, Assali *et al.* (12) report that blood

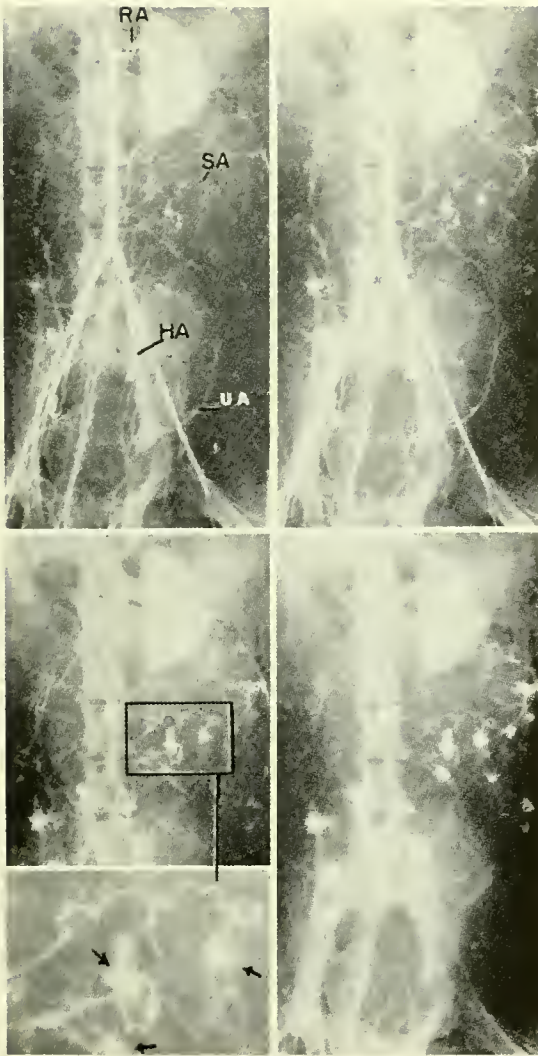


FIG. 25. Pattern of distribution of radiopaque dye injected into aorta by way of femoral artery in the monkey pregnant for 111 days. Serial radiographs taken at 3-1/2, 4, 5, and 6 sec after start of injection. Insert at lower left is of marked out portion of picture above, enlarged 4 times. The arrows indicate spurts of dye in the intervillous space. SA, spiral arteries of endometrium; HA, hypogastric artery; UA, uterine artery; RA, renal artery. [Permission of Ramsey (188).]

flow values determined by the electromagnetic flow-meter and the nitrous oxide method were in good agreement. Uterine blood flow increases from 50 ml per min in the 10th week of gestation to 190 ml per min at the 30th week. The flow of blood per unit of uterine tissue was determined to be relatively constant throughout pregnancy. The rate of increase in the rate of blood flow and oxygen consumption of the "uterus" exceeds that of the fetus; it is surmised that the placenta absorbs the difference.

A number of studies of placental blood flow in women have been reported. Browne & Veal (44) were the first to use the injection of Na^{24} for this purpose. They injected it into the intervillous space of normotensive and hypertensive women and estimated in the former a flow of 600 ml per min; in the latter, about 200 ml per min. Similar differences were found in the uptake of Na^{24} in the myometrium by Johnson & Clayton (118). Variations in growth of the conceptus and associated changes in shape of the uterus affect markedly uterine and placental blood flow [Browne (43)]. After fetal death, the placenta cannot be localized by the Na^{24} method; placental blood flow must decrease substantially. In later pregnancy, the placental flow of the maternal blood exceeds by three times the flow necessary to maintain the fetus. The work of Browne (43) likewise suggests that as maternal blood pressure diminishes in normal patients, placental blood flow increases by some enhancing mechanism, perhaps the A-V shunt of Burwell. This is presumed to be a protective mechanism, analogous to a renal shunt type of mechanism. The intervillous space pressure is equal to that of amniotic fluid pressure or very close to it [Alvarez & Caldeyro Barcia (3), Prytzowski (178), Hellman *et al.* (102)]. Interestingly, fetal capillary blood pressure in the placenta is considerably higher [Reynolds (202)]. It is probably the association of several factors that permits the escape of fetal blood constituents into the intervillous space, and into maternal blood. One is the high fetal capillary blood pressure just noted. Another is the progressive thinning of the trophoblast layer as the placenta ages, with loss of the cytotrophoblast layer and with the capillaries coming to lie next to the thin syncytium. Still another is the ever diminishing size of the villi as they increase in number. Combined, these factors permit some escape of fetal erythrocytes into the maternal circulation [Naesland (159), Mengert *et al.* (151), Bromberg *et al.* (42)]. Maternal erythrocytes do not normally enter the fetal circulation [Mittelstrass & Horst (155)]. How the exchange of water and other substances occurs between the maternal circulation where the pressure is low and the fetal circulation, where the pressure is high, has been considered theoretically by Wilkin (243, 244). Under certain conditions, simple diffusion occurs; under others, the process depends upon active transport mechanisms [Huggett & Hammond (116)].

The connection between maternal uterine blood and amniotic fluid is still a moot question, despite intensive study. That there is a rapid and voluminous

FIG. 26. Pattern of distribution of India ink in monkey placenta perfused by way of the aorta. [Permission of Ramsey (183).]



interchange is not questioned [Flexner & Gellhorn (80), Hellman *et al.* (101), see Reynolds (198) for review]. It was shown long ago [Paton *et al.* (170)] that the volume of amniotic fluid in any species is nearly constant at any given stage of normal pregnancy [Hammond (94), Reynolds (198), Lell (134), Wislocki (249), McCafferty (146)]. Although some amniotic fluid surely passes from the fetus to the amniotic sac [Reynolds (201)], water passes by an extraplacental route as well [Paul *et al.* (171)]. Moreover, maternal emboli of amniotic fluid detritus are known to occur [Bachman (14)]. Sfameni (219) has reviewed the lymphatic circulation in the vascular relations between the mother and fetus. The theo-

retical aspects of the subject are reviewed by Plentl (174, 175) and McCance & Dickinson (147).

Knowledge of the manner by which maternal blood reaches the placenta has received much study in recent years. Maternal blood reaches the placenta, of course, by endometrial branches of the uterine arteries. Blood is drained from the placenta by endometrial branches of the uterine veins. These are largely anatomical studies based upon injection of India ink or other media into the aorta or the femoral vein followed by sections and study of the injected regions [Ramsey (181)]; by injection-corrosion preparations; and by serial radiography [cf Ramsey *et al.* (188)]. Direct injections of uterine vessels of excised

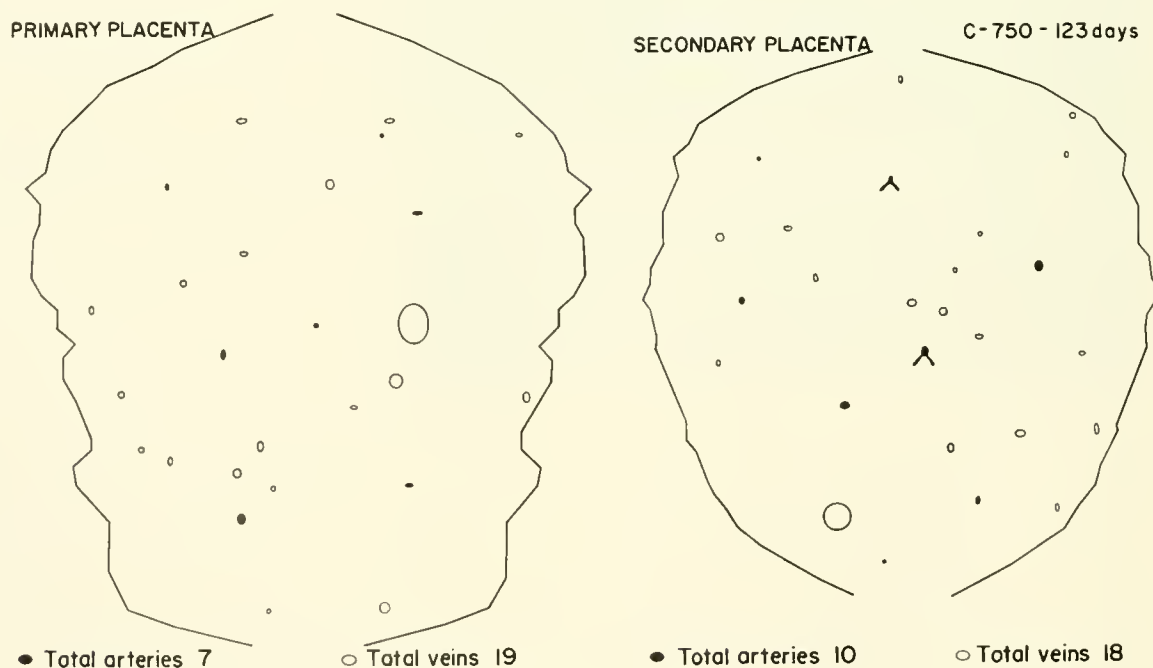


FIG. 27. Total arterial and venous openings in the placenta of the monkey in late pregnancy. [Permission of Ramsey (184).]

pregnant uteri have also been made. Evidence shows that the blood enters the intervillous space of the placenta in spurts and diffuses into relatively localized areas where, circulating about the placental villi, it leaves the spaces by nearby veins. However, simultaneous blood samples from different parts of the intervillous space yield the same blood oxygen levels [McGaughey *et al.* (148)]. There is no appreciable Spanner type of circulation toward the chorial plate and then to the margin of the placenta where it is carried off through a marginal sinus. The latter structure does not, in fact, exist. There are veins that drain various parts of the margin of the placenta but veins also drain the basal plate and the septa as well.

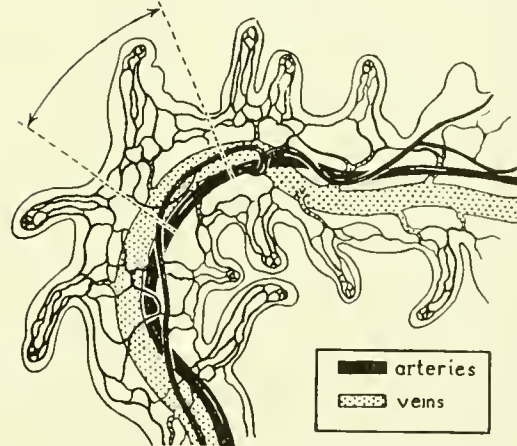
The number of vessels supplying the placenta has received recent attention. The number of arteries emptying into the placenta in late pregnancy per unit area is less than at an earlier time [Boyd (41)]. The number of arterial openings into the human intervillous space is about 300 for 25,000 mm² at term and about 120 for 6000 mm² in the fourth month. Moreover, the lumens of the arterioles are much reduced in size by an accumulation of intimal tissue near the orifice [Ramsey (184)]. In elephantulus, each placenta is supplied by three small arterioles [van der Horst (114)]. The number of veins draining the placenta is about double that of the arteries [Ramsey (182, 186)]. Radiographic (serial) studies of the entry of blood into the placenta are reported in monkeys [Ramsey *et al.* (188)] and women [Borell *et al.* (38, 40), Fernström (79), Hörmann (111), Hartnett (97)].

The question of the pathway of maternal blood flow vis-a-vis the fetal blood flow in the hemochorial placenta has received consideration. Barcroft & Barron (18, 19), Wimsatt (248), and Mossmann (158) incline to the view that incoming maternal arterial blood (oxygenated) encounters incoming fetal blood (reduced) and, running parallel to the point at which the streams part, the maternal blood gives up oxygen to the fetal blood along the way. Noer (161) has shown this to be true in an artificial model when acid ions, dyes, and dextrose are used. To apply the principle of countercurrent flow to the hemochorial placenta, as Spanner (224, 225) has done, is in error, as a number of observations show [Stieve (226), Ramsey (183, 185), Fernström (79), Borell *et al.* (39), Hilleman (107), Kladetzky-Haubrich (129)]. It does not apply in the labyrinthine placenta of the rat [Hamilton & Boyd (92), Bøe (32, 33)] or hamster [Adams & Hilleman (1)], or in the placenta of the sow [Amoroso (4)].

Extensive studies of the arrangements of fetal cotyledons and of the blood vessels within them have been made. The gross vascular arrangement in the hemochorial placenta shows the cotyledon to be a tuft, arising from a single stem artery. It sends anchoring branches to the basal plate. Free villi are given off from the anchoring villi and from recurrent free villi that pass toward the chorionic plate from the anchoring sites [Wilkin (244), Crawford (54)]. Gross relations are described by Falkner (75), Earn & Nicholson (68), Crawford (56), ten Berge (232), Thoyer-Rogart & Harris (235), Vernete & Esteban-Caballera (236), Lemtis (135), Danesino (60, 61), and La Haye (133). One author claims the fetal vessels are densest near the decidual plate [ten Berge (232)], but this is denied by Beker & van Steenis (29).

Vasculature of human chorionic villi

(after Bøe)



Superficial capillary network

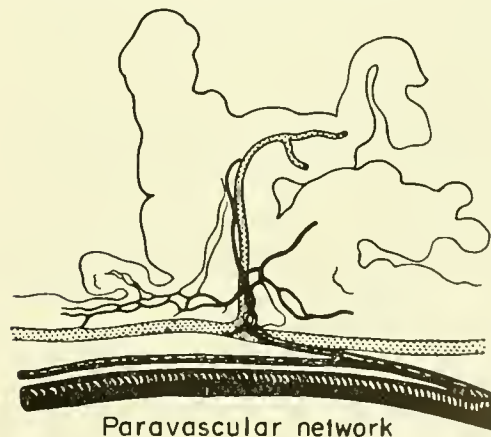


FIG. 28. Schematic representation of major and minute vessels in villus of human placenta. [Permission of Bøe (33).]

and Crawford (56). Within the fetal villus, the essential vascular arrangement is one of a large plexus rather than a series of simple capillary networks [Crawford (56), Bøe (33-35)].

In concluding a review of the maternal blood flow in the uterus it is appropriate to note that where the pregnant uterus is concerned, the fetal circulation cannot properly be separated from the uterine cir-

culation. They are a complex and in a sense a single unit, one affecting the other in the developing changes that take place. The conceptus affects uterine growth and all that that entails, while at the same time the uterus affects the development of its contents. The complexity of the relationships between uterine growth, vascularity, and fetal development are reviewed elsewhere in this context (203).

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The fetal and neonatal circulation

MAUREEN YOUNG *Department of Medicine, St. Thomas's Hospital, London, England*

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THIRTY YEARS HAVE PASSED since the inspiration and eloquence of Sir Joseph Barcroft gave the functional development of the cardiovascular system its place in circulatory physiology. In the intervening years histochemical techniques and the electron microscope have shown how complex is the placental structure between the maternal and fetal circulations: advances in knowledge of transport mechanisms and the use of isotopically labeled compounds begin to clarify the active processes occurring within this structure: the pathways of the circulation "in utero," in both the placenta and the fetus, and the changes of the latter at birth, have been confirmed: studies of the development of the regulatory mechanisms of the fetal circulation have been extended into the neonatal period (70, 83); finally, obstetricians and pediatricians have accumulated circulatory information on the human infant which demonstrates the value and limitations of applying observations from one species to another. Detailed reviews have been written on each of these subjects both from the historical viewpoint and that of comparative physiology: it falls to this chapter to do justice to the main facts with particular reference to the higher mammals and to the human infant.

In acute experiments on the fetus with an intact placental circulation, the possibilities of departure from the physiological state are even more numerous than in the grown animal. Understanding of the precise influence of the disturbances due both to the anesthetic and to removal from the uterine environment awaits the development of intrauterine techniques such as the chronic implantation of electrodes and catheters. Many workers have tried to minimize these disturbances by working on the fetus delivered into a saline bath at 37°C; however, particular attention must be paid to the position of the fetus in relation to the placenta; further, interference with the maternal

placental blood flow and therefore the internal environment of the fetus, consequent upon the retraction of the cut uterine muscle around the uterine vessels, still occurs. In the sheep, on which many of the studies have been made, the uterine muscle is not so reactive to mechanical stimuli as the uterus of the rabbit, the guinea pig, or the monkey and man. Spasmolytics have not been used to prevent this response of the uterine muscle. The local application of procaine or papaverine is used to prevent spasm of the umbilical vessels during cannulation or sampling of blood, but these maneuvers are best carried out on the abdominal trunks of the vessels, which are less contractile, or on the placental tributaries, in order not to interfere with the main blood flow.

Barcroft's (25) theme that it is dangerous to argue from species to species about the relative stage of physiological development in utero and at birth is most applicable to a consideration of the cardiovascular system. It will become apparent that, in the species which have been most extensively studied, functional development does not depend upon gestational age but corresponds most nearly to the requirements of the newly born when it is, however, never so advanced as in the adult.

THE FETAL PLACENTA

Implantation

What forces compel the fertilized ovum to satisfy its high nutritive requirements in the superficial layers of the endometrium? Or does the endometrial epithelium have the power to attract inert particles the size of the 7-day human blastocyst (106)? What are the mutual relationships between the trophoblast

and the endometrium once contact between the two has been established? Both the anatomical and experimental aspects of implantation are beautifully described, for many species, by Hamilton *et al.* (102) and by Boyd & Hamilton (45). Under normal conditions the blastocyst in utero implants at a definite size, at a prescribed time, and in special sites (43); the presence of progesterone is essential but the mechanism of its action is unknown (148). Fawcett *et al.* observe that, "the individual potentialities of the ovum and uterine mucosa should not be thought of as mutually exclusive but mutually supporting and neither is 'chiefly' responsible for implantation" (94). These potentialities may, however, be observed quite independently: the mouse ovum, once it has reached a certain size, is capable of implanting randomly in extrauterine sites such as the anterior chamber of the eye and the abdominal cavity, regardless of the sex of the host. The trophoblast causes extravasation of blood in these sites before cellular invasion has taken place and the substance responsible must be actively penetrating, for secondary implantation sites start to proliferate in the macaque before any erosion of the uterine surfaces (191) and, in the human, congestion also appears on the opposite side of the uterus to the site of implantation (105). The active substance may be a product of metabolism of the dividing blastocyst, even carbon dioxide itself; or it may be chorionic gonadotrophin, known to appear first at the time of implantation. Evidence for a penetrating action of chorionic gonadotrophin is suggested by perfusion experiments on full-time human placentas; citrate metabolism is enhanced by estradiol only when chorionic gonadotrophin is also added to the perfusing fluid (180). The initial responses of the endometrium may also be observed in

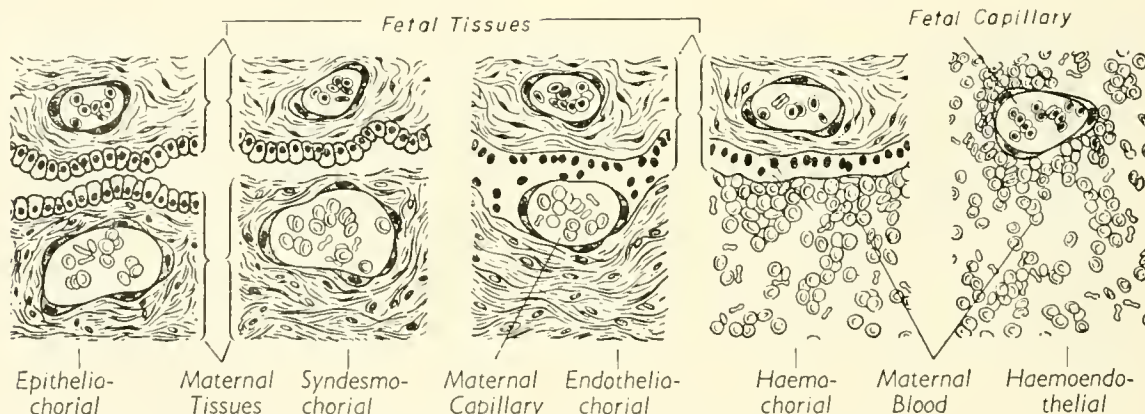
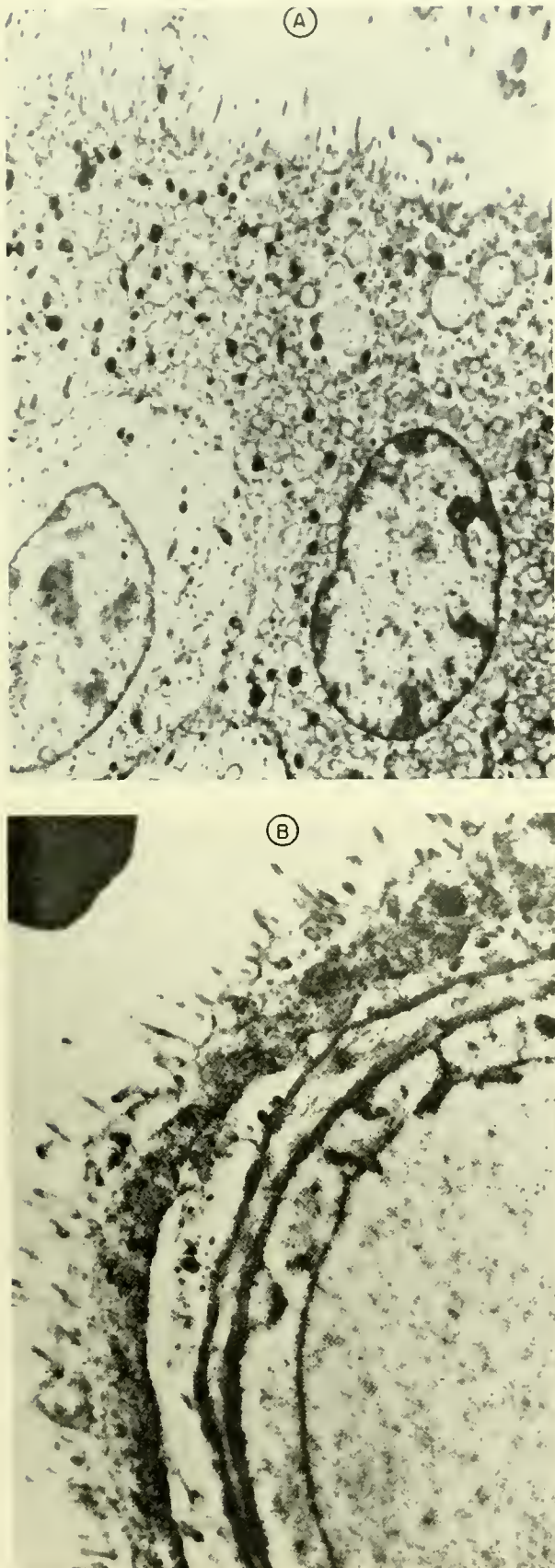


FIG. 1. Histological types of placenta arranged to emphasize the progressive breaking down of the barrier between the maternal and fetal circulations. [Redrawn by Amoroso (8).]



the absence of a fertilized ovum. In the rat, but not in the guinea pig, the endometrium is able to implant inert objects, such as glass beads the size of the blastocyst normally implanted (36). Electrical and mechanical stimulation of the pregnant rat uterus can produce the formation of a maternal placenta, identical in structure with the decidua of pregnancy; these deciduomata may bleed into the uterine cavity and the early normal extravasation of blood in the endometrium is therefore probably not dependent upon the fetal trophoblast (125, 170).

The implanted blastocyst probably receives its nourishment for a short time from the glycogen, lipid, and other materials stored in the stromal cells of the uterine mucosa which have become enlarged by the decidual response; in some ruminants the mucosa secretes uterine milk for this purpose. The formation of the true placenta, containing the fetal and maternal circulations is due to a balance in activity of the fetal trophoblast and maternal decidua; any disturbance in this balance may result in the rejection of the blastocyst or nonspecific, even malignant, growths. Progesterone and estrogen are required for placental and fetal development, the ovary and placenta itself contributing to the production of these hormones to varying extents in the different species (10): an adequate placenta may develop in the peritoneal cavity and viable infants be delivered at laparotomy (81); it has been shown in the mouse and the cat that the fetus is not necessary for the development of the placenta (11, 141).

Placentation and Placental Function

Amoroso (8) describes fully the structure of the tissue which separates the fetal from the maternal blood streams in mammalian placentas, following the classification of Grosser (100) modified by Mossman (138). Figure 1 demonstrates how this scheme is based on the number of tissue layers between the two

FIG. 2. *A*: section through a villus from a human placenta of 9 weeks gestation. ($\times 7,040$.) The surface projections and a bulbous promontory are illustrated. In the apical part of the syncytium some large vacuoles, filled with granular material, are seen. These are interpreted as absorption vacuoles formed by pinocytosis. They are different from the smaller vesicles with homogenous centers which are thought to be ergastoplasmic. *B*: section through a thin portion of a human villus from a placenta delivered at term. ($\times 10,110$.) There are well-developed microvilli on the surface of the syncytium. Beneath the syncytium is a zone of lighter cytoplasm. Such a zone has been shown to be continuous with residual Langhans cells. The basement membranes are present, separated by a space in which collagenous fibrils can be seen. Beneath the second of these is the endothelium of a fetal capillary. [From Amoroso (9).]

circulations. The "thinner" placentas start with six cell layers between the maternal and fetal blood, as in the epitheliochorial placenta, and there is a progressive breakdown of tissue during development which chiefly involves the three maternal layers. Figure 2A and B shows that, even after the number of cell layers has been determined in the human placenta, there is a further reduction in depth of the remaining tissue. The thickness of this placental "barrier" will be one of the factors influencing the rate of transfer of substances, such as the respiratory gases, water, and electrolytes, dependent upon simple diffusion for their transfer; but most of the exchanges between the mother and fetus will take place by active transport, and the composition of the cytoplasm rather than the depth of the barrier is likely to be the more important factor (63, 143); the evidence suggests that placental tissue has a high oxygen consumption, 10 ml per kg per min, probably higher than the fetus itself (17, 111). Histochemical techniques have identified the cytoplasmic content of the cells with a variety of proteins, enzymes, lipids, and carbohydrates (8, 190); the cytoplasmic structure is transient, and changes as the functional capacity of the fetal metabolic processes develop during gestation (181). The varying structure of the barrier in different

species has been a constant target for speculation and probably represents adaptations concerned with differences in intermediary metabolism and the required rate of growth of the fetus.

In the hemochorial placenta, in which the maternal endothelium is absent, vesicles of maternal plasma may be transported across the trophoblastic cells into the fetal blood stream; these vesicles are formed by a fusion of the microvilli of the syncytium, or pinocytosis (128), and probably enable the transfer of whole protein molecules, possibly those responsible for the passive immunity of the fetus (22, 64). Other special mechanisms occur in the pregnant uterus for transferring materials to the fetus; the fetal membranes in the rabbit are able to transfer immune proteins, secreted by the uterine glands (46) and the endometrial cups of the pregnant mare secrete gonadotrophin (9).

Finally, the functional capacity of any placenta will also depend upon the maternal and placental blood flows. In most animals the number of chorionic villi and the placental weight increase rapidly after implantation and reach a maximum while the fetus is differentiating and before the major increase in weight gain (25). The opportunity for exchange between the two circulations will be limited by the efficiency of these chorionic villi, the disposition of the maternal and fetal blood vessels in relation to each other, and the blood flows on either side of the placental barrier. Bumm (48) suggested that a countercurrent flow mechanism might exist to facilitate exchange across the barrier in the human placenta, and Mossman (137) demonstrated that suitable anatomical arrangements of the blood vessels were, in fact, to be found in the ground squirrel and in the rabbit. Figure 3 shows the probable direction of the two blood streams in the sheep; fetal blood, passing through the chorionic vessels has the opportunity of exchanging with the maternal arterial blood before leaving in the umbilical vein for the fetus. Similar arrangements exist in all species with a labyrinthine placenta (8). In the hemochorial placenta of the primate the principle of countercurrent flow is insured functionally: the maternal arteries enter the intervillous space through funnel-shaped openings, and the blood is projected up to the base of the chorionic villi to exchange with fetal blood leaving for the umbilical vein (153). There has been much controversy over this circulation through the years but recently elegant radiological demonstrations by Borell *et al.* (38) in the human, and by Ramsey (153) in the macaque

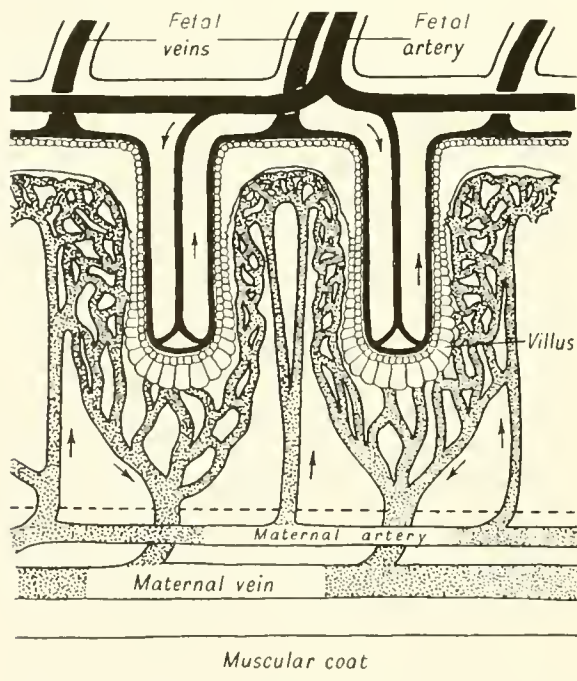


FIG. 3. Arrangement of blood vessels in the placentome of the sheep placenta. [Redrawn by Amoroso (8) after Barron.]

monkey, leave little doubt that there is a blood flow mechanism in these placentas which approaches the efficiency of the countercurrent methods (31).

EARLY DEVELOPMENT OF THE CARDIOVASCULAR SYSTEM

Streeter's label for the fetus as a whole, "Open for business during alterations" is most readily extended to the cardiovascular system: this is the first organ system to reach a functional state in the embryo, it supplies all the embryonic tissues and undergoes rapid and extensive alterations during the development of the organs.

Peripheral Circulation

Again, Hamilton *et al.* provide a detailed account of the morphology of the development of the mammalian cardiovascular system (102). But, what determines the appearance of isolated endothelial cords, first in the yolk sac area, and then in the embryo, with the eventual formation of diffuse plexuses? Why do lumina develop in these cords and why do larger channels form? What is responsible for the elaboration of the neighboring mesenchyme into the tunica media and adventitia? Why does the heart form and become differentiated to direct the blood through these channels? None of these questions can be fully answered but, following the study of the histogenesis of the arteries in the chick embryo, Hughes discusses the many factors which can influence the development of blood vessels (113). The primitive endothelial network is formed before the circulation begins and is determined by genetic factors: in contrast, the development of the main vessels within the capillary network is dependent upon a circulation and the dynamic relationship between the structure of vessels and the rate, direction and pressure of blood within them is probably acquired early in embryonic life. There are no hemodynamic measurements with which to substantiate this statement, but the classical relation between function and structure is to be found in Benninghof and Spanner's description of the acardiac fetus with a normal twin (35); all the arteries of the acardiac fetus, including the aorta and common carotid, possessed the structure of peripheral muscular vessels because they were physiologically peripheral arteries of the normal

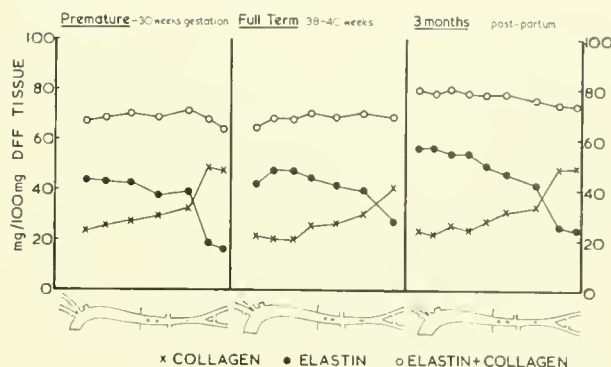


FIG. 4. The pattern of fibrous protein distribution in the major vessels of the human infant at 30 weeks gestation, full term, and 3 months post partum (Cleary, unpublished).

twin, whose heart circulated the blood in both fetuses. The mammalian ductus arteriosus, on the other hand, is a particular example of a muscular artery joining two adjacent elastic arteries. The adult pattern of fibrous protein distribution is present by 30 weeks in the major vessels of the human fetus (fig. 4); elastin exceeds collagen in the thoracic aorta but the proportion of each is reversed in the abdominal aorta. The percentage of elastin increases to a maximum 3 months after delivery.

The capillary networks are coarse in young embryos and become more delicate and numerous during development, but at different times in the various tissues (142, 152) and it would be instructive to correlate the degree of vascularization with the oxygen requirements of the organs. The richness of distribution of the capillary bed will be of special importance in the lungs, brain and cardiovascular system of the prematurely born and postmature young.

The Heart

Ebert *et al.* describe the initial phases in heart formation, from experimental evidence in the chick and rat embryos (87, 96). In the prestreak embryo the capacity for heart formation is widely distributed and pulsating cardiac muscle may develop in tissue culture of peripheral and posterior regions of the blastoderm: later, this capacity is more restricted and is finally limited to two definite regions which subsequently fuse in the head process stage embryo. In vitro these cells will develop into a rounded mass of cardiac muscle and the onset of contractility is swift and associated with the appearance of glycogen, but not with definite myofibrils or cross striations.

But the morphogenesis of heart chambers can only take place "in embryo" demonstrating, again, the probable importance of spacial factors in development; striated myofibrils are present by the time the contractile activity is sufficient to circulate the blood. Ebert (86) has shown by immunochemical techniques that cardiac myosin, similar to that found in the adult, is widely distributed in the very early embryo and that the restriction of the heart-forming area during development is accompanied by a limitation of the synthesis of this specific protein and the commencement of the capacity for synthesis in these areas. These facts do not explain the first appearance of myosin or actin, the origin of the nonpropagated contractions which begin in the ventricles, or the probable dependence of the developing cardiac muscle metabolism chiefly upon anaerobic glycolysis (177).

Congenital Malformation

A knowledge of the metabolic processes responsible for embryonic differentiation would provide the foundation for a better understanding of the causes of congenital malformation and help to enable their prevention. In human pediatrics, congenital abnormalities appear in 1 per cent of all live births (162) and now contribute to 20 per cent of the neonatal deaths in countries where the infant death rates are low (185); malformation of the cardiovascular system is second to malformation of the nervous system in causing this mortality. The causes of congenital abnormality may be genetic but are chiefly due to environmental factors (147) and there is a wealth of descriptive information on the influence of a wide variety of experimental procedures and chemical substances which are teratogenic (119); each is usually effective at a certain stage of development and may influence the organogenesis of one or a number of the systems. Abnormalities of the cardiovascular system in human infants are mainly associated with the rubella virus: in the experimental animal metabolic inhibitors and nutritional deficiencies of the mother, especially of the vitamins, may produce abnormalities; the high concentration of riboflavin in fetal blood and the transfer mechanism which exists in the placenta for this vitamin is probably related to its high requirements in fetal metabolism (131). Acute anoxaemia, due to maternal exposure to carbon monoxide gas is known to be teratogenic in the human infant (115) but chronic hypoxia, though it may be effective in animals (119), is diffi-

cult to establish as teratogenic in the human. The incidence of congenital malformation of the cardiovascular system is no greater in infants born to women living at high altitudes than it is at sea level (147), demonstrating that the adaptive processes enabling life at lower oxygen tension also ensures an adequate oxygen supply in developing tissues. Another aspect of chronic hypoxia, reduction in maternal placental blood flow, probably has most important consequences for the infant in such conditions as toxemia of pregnancy: in animals a reduced maternal placental blood supply causes "runting" and the over-all size of the fetus is small, but there appear to be no definite congenital abnormalities (132); this may possibly be explained by the reduction in supply of nutritive material without any alteration in balance of the essential constituents. These epidemiological and etiological facts cannot, yet, explain why only 5 to 30 per cent of the infants, born of mothers infected with rubella during the first trimester, develop malformations of the cardiovascular system (95) or why the disturbance of organogenesis presents itself in diverse forms. For example, why does normal but misplaced growth of the large blood vessels occur? What stimulates growth of the septum secundum causing premature closure of the foramen ovale and why is there too little reabsorption of the septum spurium leaving Chiari's net (144)?

COURSE OF THE CIRCULATION IN THE FETUS

The probable course of the fetal circulation in the mammal, once the major channels have developed, is illustrated in figure 5. The most arterial blood circulates from the placenta, in the umbilical vein, to the liver which it perfuses; this blood leaves the hepatic vein to join venous blood from the caudal part of the body in the inferior vena cava. In some species, notably the human, the monkey, and the sheep, a proportion of the blood in the umbilical vein short-circuits the liver and passes straight into the inferior vena cava through the ductus venosus. As it enters the heart the inferior caval stream is divided by the crista dividens of the foramen ovale (fig. 6); most of the blood flows straight into the left auricle, where it mixes with a small volume of pulmonary venous blood and passes into the left ventricle, whence it is pumped mainly to the head and upper extremities. A smaller stream of inferior caval blood is directed to the right auricle, mixes with venous blood from the coronary sinus and from the

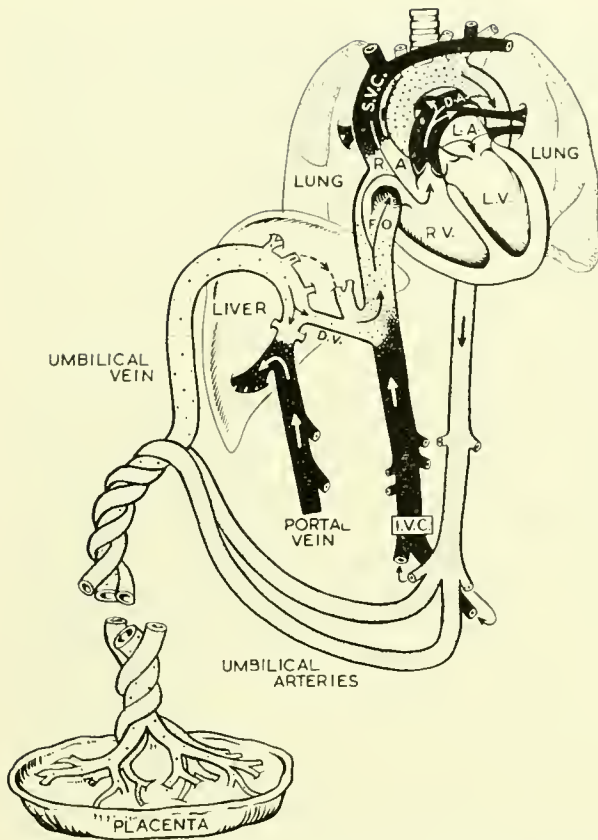


FIG. 5. Fetal circulation and probable course of the blood through the fetal heart. [After G. S. Dawes (Bell *et al. Textbook of Physiology and Biochemistry*, 5th ed., 1961).]

upper part of the body, carried by the superior vena cava, and passes into the right ventricle; most of this blood short-circuits the lungs, through the ductus arteriosus, and passes to the descending aorta to supply the lower extremities or become oxygenated in the placenta.

The presence of the ductus arteriosus and the foramen ovale and their functional significance, allowing the two ventricles to work in parallel, did not escape William Harvey: "Thus, in the embryo, while the lungs are idle and devoid of activity or movement, as though they did not exist, Nature uses the two ventricles of the heart as one for the transmission of the blood." Harvey used the fetal circulation to support his general thesis of the circulation of the blood. Barclay *et al.* (27) review the history of the anatomical evidence for the present concept of the fetal circulation: Sabatier, nearly two hundred years ago, observed that the foramen ovale did not lie between the two atria, but at the junction of the two venae cavae with the left auricle, and directed the inferior caval blood into the left auricle; it was he who

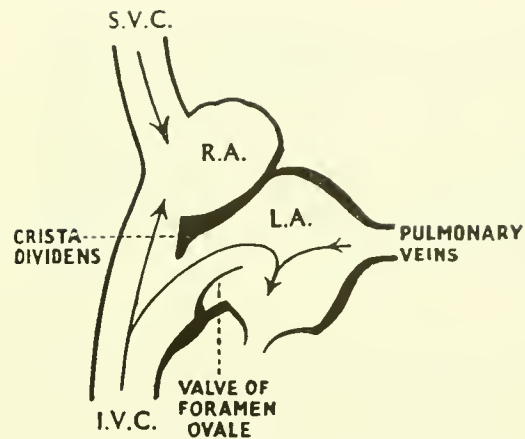


FIG. 6. Diagram of the great veins to show that in the fetus the inferior vena caval blood divides into two streams, one of which enters the right atrium while the other passes through the foramen ovale into the left atrium. [From Dawes (66).]

first suggested the figure-of-eight-like course for the circulation shown in figure 5. Shortly afterwards, Wolf also found that the two atria were not in communication with each other, that the inferior vena cava lay between them with openings in each, and that the relationship of these communications was such that the major portion of the inferior caval stream would pass into the left auricle. It was not until 1939 that the pathways of the inferior and superior caval streams, in the chest and heart, were actually observed in the sheep by Barclay *et al.*, using rapid serial radiography following the injection of radiopaque substances (26). Similar observations have been made, most elegantly, in the full-time human infant by Lind and Wegelius who were able to make the injections and perform the angiocardiology before the first breath (129). The latter have also confirmed the functional relationship between the venae cavae and the atria in early nonviable infants at therapeutic abortion.

Regional Blood Flow

Was Sabatier correct in suggesting that the brain is supplied by the most arterial blood? How much mixing is there of the superior and inferior caval blood in the right auricle? How much pulmonary venous blood is added to the inferior caval blood in the left atrium? Huggett, who was the first to carry out experiments on the living fetus with an intact placental circulation, found that the oxygen content of the carotid artery exceeded that of the umbilical artery in goats (112); Barcroft observed a 10 to 20 per cent

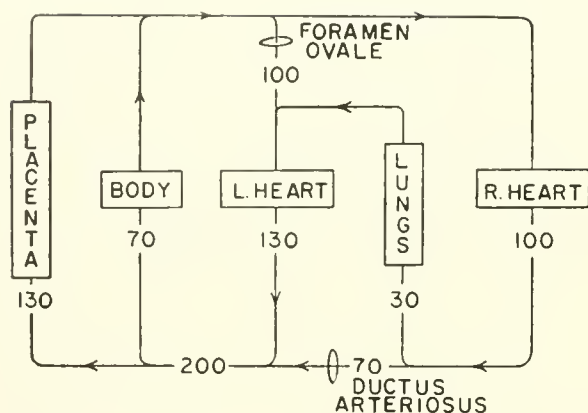


FIG. 7. To show that both sides of the fetal heart work in parallel; the approximate volume of blood flow through the principal vessels, in the lamb, is indicated in ml/kg/min. (From G. S. Dawes. Changes in the circulation at birth. *Brit. Med. Bull.* 17: 149, 1961.)

difference in saturation in favor of the carotid artery in the sheep (25). Everett and Johnson injected labeled phosphorus into the superior or the inferior vena cava and, from its partition in the left and right atria, were also in favor of the Sabatier hypothesis (91). Evidence which suggests that the upper half of the body may require a better oxygen supply is provided by Spratt who added metabolic inhibitors to the developing chick embryo *in vitro*; he concluded that the developing nervous system depended primarily upon oxidative metabolism, in contrast with the heart which depended chiefly upon anaerobic glycolysis (177). It was also shown, by tissue slice technique in the sheep that the requirements of the brain per gram of tissue increased during the last third of gestation but that the proportional oxygen uptake of the brain per kg of body weight remained constant, at about five times the adult value (53).

Eränkö and Karvonen, however, could find no difference in the number of hemopoietic foci between the lower and upper limb bone marrow of fetuses which might be expected if the oxygen tensions of the two bloods were different (90). Dawes and his colleagues observed that the oxygen content of the carotid artery only exceeded that of the umbilical artery by 6 per cent, when both were sampled simultaneously, in the lamb (76) and the monkey fetus (71); greater differences were observed following hemorrhage, constriction of the umbilical cord, or hypoxia, especially in young fetuses (68). These observers also approached the problem more quantitatively by estimating, simultaneously, the oxygen content of the blood in the two venae cavae and, after the two streams have mixed, in the pulmonary

trunk in the sheep at term. Similar analyses were applied to the three other positions in the fetal circulation where blood of differing oxygen content meet, namely the upper part of the inferior vena cava, the left atrium and the junction of the ductus arteriosus with the descending aorta. From these measurements they were also able, by making certain assumptions, to calculate the blood flow in all the principal vessels as a fraction of the cardiac output (fig. 7): they concluded that the similarity of the oxygen content of the blood supplying the upper and lower extremities could easily be accounted for. Measurements of the regional blood flows and oxygen utilizations are needed to prove the hypothesis that the course of the circulation in the fetus is designed to ensure the supply of the most arterial blood to the brain and coronary circulation.

The blood flow through the various fetal organs and through the placenta will vary both quantitatively and relatively to one another during growth, and this theme has been well developed by Barcroft (25) and Barron (28). What are the relative proportions of the cardiac output which perfuse the fetus and the placenta? What is the magnitude of the pulmonary blood flow during development? Barcroft & Kennedy (24) found the relative distribution of the blood between the fetus and the fetal placental circulation in the sheep to change during growth in such a manner that when the embryo was young, the greater part of its blood volume was in the placenta; halfway through gestation, when the placenta had reached its full size, the position was reversed and the amount of blood in the placenta remained constant while that in the fetus increased. The anatomical limit having once been set, the rate of turnover of the blood in the placenta will become increasingly important and the fetal heart does not "keepe holiday" (William Harvey) but has an increasing responsibility to meet the demands of growth; the increase in cardiac output and vasomotor tone will ensure the gradual rise in arterial pressure upon which the umbilical blood flow will depend. Barcroft (25) estimated that at least 50 per cent of the combined cardiac output perfused the placenta in the goat and in the sheep near term, and Dawes *et al.* (76) calculated a figure of 57 per cent. How this proportion changes during gestation is not known. Cineradiographic observations in the sheep (26) and human infant (129) suggest that the blood flow through the fetal lungs is a small proportion of the combined cardiac output during intrauterine life. Since the development of blood vessels is dependent upon

genetic and environmental factors as well as the pressure within them, the fact that the great vessels do enlarge and the pulmonary vascular bed does increase must mean that there is an increasing volume of flow during intrauterine life; however, it is not known whether the proportion of this blood flow to the total cardiac output changes or remains constant during development. Dawes *et al.* (76) have estimated that, in the near term sheep fetus, about 10 per cent of the combined ventricular output perfuses the lungs.

Hepatic Blood Supply and the Ductus Venosus

The liver is probably supplied by the most oxygenated blood in the body; the umbilical vein carries well-oxygenated portal blood from the placenta and a hepatic branch leaves, before the ductus venosus, to supply the left lobe of the liver, nearly two-thirds of the whole organ. The volume of this flow is large, representing over 50 per cent of the cardiac output (since the umbilical blood flow is about 57% of the cardiac output in the lamb and probably only a small proportion passes through the ductus venosus), and the oxygen tension is unlikely to be greatly reduced by mixture with hepatic arterial blood. Emery (89) found more hemopoietic foci in the right side of the liver than in the left and degenerative changes are observed more frequently on the right side of the liver at autopsy in stillborn infants and following neonatal deaths (101). It is possible that the reduction in oxygen supply to the liver, following birth, is a factor in the development of physiological icterus (178).

The presence of a ductus venosus is not universal but it is patent in the lamb and monkey and in the human infant at term (27, 71, 129); at the junction with the umbilical vein, the vessel possesses a muscular sphincter, which is innervated by postganglionic branches of the vagus nerve. Cineangiography suggested to Barelay *et al.* (26) that only a small proportion of the umbilical venous blood flow passed through the ductus venosus in the lamb but no direct measurements have yet been made. It has been suggested that the sphincter closes in response to a rise in umbilical venous return to the heart (155); conversely it may regulate hepatic blood flow itself or the placental blood flow since the main resistance to the umbilical blood flow resides in the liver. A large flow through the ductus venosus would ensure a good supply of arterialized blood to the head but the fact that a ductus venosus is not always present suggests

that no special mechanism exists for supplying the brain with the most arterialized blood. Experimental occlusion of the ductus venosus in the mature lamb, caused no significant change in arterial blood pressure, heart rate, or carotid arterial O₂ saturation (12). Rostral to the ductus venosus the umbilical vein continues as the portal sinus and joins the portal vein where arterialized and venous blood meet in unknown quantities.

FETAL HEART

The development of activity in the mammalian heart has been observed in hanging drop cultures of whole embryonic rat vesicles (96): the earliest contractions occurred in the left ventricle and were followed by a slower rhythm in the right ventricular tube; when the two ventricles joined the left became the pacemaker. The auricles beat a little later and the sinus venosus last, finally bringing the ventricular rhythm under their control at an early stage in development.

Recording of the electrical activity of the heart in utero has not been frequently attempted in experimental animals but would provide both fundamental knowledge of the development of the propagated impulse and enable the fetal heart rate to be counted with minimal disturbance during growth. The impulse is large enough to record in rabbit and guinea pig fetuses, 15 g in weight (32, 133). Recording of the ECG of the human fetal heart in utero, using leads placed in the mother's vagina or rectum, or on her abdomen has been employed for many years to monitor the heart rate, particularly during difficult labors (127); the method is not, however, widely used and it is possible that the electrophonocardiograph will be simpler and less subject to interference from the maternal heart (175). Electrocardiograms obtained from human infants at Cesarean section show all the deflections characteristic of the adult as early as the second month; in the full-term infant there is a small right ventricular preponderance corresponding to the slightly greater relative weight of this ventricle at birth. The left ventricle starts to exceed the right 3 months after birth and by 6 months of age the deflections are usually identical with those of the adult; this is due both to growth of the left ventricle and to involution of the right ventricle (121). The T wave is frequently of low amplitude at birth and becomes negative shortly afterward (178); the sign may be reversed again by the administration

of adrenaline and the observers attributed this to a rise of pulmonary arterial pressure.

Heart Rate. Regulating Mechanisms

In the smaller animals systematic correlation of the fetal heart rate with age has not been frequently made and when the uterus is opened the data may be questionable on account of cooling and hypoxia (189). In the guinea pig and the rabbit the heart rate has been counted from ECG records taken with the uterine wall intact and the maternal abdomen opened under saline at 37 C (133); the heart rates in both increased from 160 to 320 per min during 20 to 67 days in guinea pig and 25 to 31 days in the rabbit fetuses, but the range was wide, possibly on account of intrauterine hypoxia. The maternal heart rates also varied widely and within the same range as the full-term fetus. In the guinea pig fetus a slight slowing occurred when the uterine wall was incised and allowed to contract around the large vessels supplying the placenta. In the rabbit fetus postmaturity did not influence the heart rate (134). The heart rate of the monkey fetus at Cesarean section is 140 to 170 beats per min (71).

Barcroft and colleagues (25) counted the lamb heart rate in utero with a stethoscope and found that it increased during the first two-thirds of pregnancy to 150 beats per min and thereafter fell slowly to 128 beats per min at term; in a larger series in which the heart rates were obtained from blood pressure tracings, the rate rose throughout gestation to about 200 beats per min at term (39). The ewe heart rate is normally 100 to 120 per min. In two studies in humans the fetal heart rate was also observed to be faster in midfetal life, 156 per min, than just before birth, when the average was 142 per min. These differences are small, however, and probably not significant; in one study the counts were made with a stethoscope (176) and in the second from ECG recordings (192).

The pattern of changes in fetal heart rate in utero will be determined by the rate of development of the pacemaker rhythm and the onset of subsequent vagal restraint. The anatomical pathways of the parasympathetic system are laid down early, and vagal fibers may be observed in the A-V bundle in a 6-weeks-old human fetus (184), before the inhibitory response of the isolated cardiac muscle to acetylcholine is observed (194). Vagal tone is not apparent in utero or subsequently in the guinea pig, rabbit, or cat: the full-term fetal heart rates are the same as in the adult,

and in the cat the heart rate is uninfluenced, in both the newborn and the adult, by section of the vagus nerves (114); the latter, however, is not particularly good evidence. Vagal tone was considered by Barcroft and colleagues (25) to be present in the sheep fetus toward term, for they found that bilateral section of these nerves increased the heart rate; this, however, was not confirmed by Born *et al.* (39). Stimulation of the peripheral cut end of the vagus nerve will cause bradycardia in the sheep fetus half-way through gestation, though the heart will respond to intravenous acetylcholine earlier (74). The isolated fetal heart is very sensitive to acetylcholine but it is not possible to correlate this with the age of the fetus (19). The influence of atropine on fetal heart rates and a comparison with its action in the adult of the same species is practically unknown; late in intrauterine life atropine in the fetal circulation causes an acceleration of the fetal guinea pig heart (97). In the pregnant woman atropine in the maternal circulation (110) abolishes asphyxial fetal bradycardia, but there is no evidence for its influence on the normal heart rate nor independent evidence for its placental transfer.

The sympathetic pathways are known to be laid down early in development in the kitten and the human fetus (44, 103); the lamb heart is able to accelerate in response to intravenous adrenaline two-thirds of the way through the gestation period and at term the sensitivity of the fetal heart is little different from that of the adult in both the sheep (74) and the rabbit (70); earlier observers frequently found a decreased sensitivity and this was possibly due to anoxia (194). Again, the isolated heart is sensitive to adrenaline and noradrenaline and there is no correlation with the age of the fetus (19).

Cardiac Output

Fetal cardiac output was measured in the goat both cardiometrically and using the Fick principle by Barcroft and his colleagues (25); they estimated that it increased from 113 ml per kg body weight per min at 89 days of age to 193 ml per kg body weight per min at 150 days, full term. Dawes *et al.* (75) calculated that the cardiac output of both ventricles in the lamb at term was 235 ml per kg per min, knowing the umbilical blood flow and estimating that it formed about 57 per cent of the combined cardiac output. Assali *et al.* (17) made similar calculations in human fetuses of 9 to 28 weeks gestation and found the cardiac output to be 200 ml per kg per min;

their assumptions *a*) that the umbilical blood flow is a constant fraction of the cardiac output during this period of rapid growth, and *b*) that the umbilical blood flow forms the same proportion of the cardiac output in both the human and in the sheep fetus have, to date, no foundation.

ARTERIAL BLOOD PRESSURE

Systemic Pressure

The rate of increase in systemic arterial pressure during gestation varies among the species and the final values at term correspond most nearly to the requirements of the newly born: for instance, in the helpless newborn of the rat and rabbit the mean pressure in the carotid artery is only 30 mm Hg after 21 and 31 days of gestation, respectively (49, 70); the newborn kitten and puppy are also born with arterial pressures of 30 mm Hg after 67 days (114) while the active guinea pig is born with an arterial pressure of 50 mm Hg after a similar time in utero. Arterial pressures of 60 to 70 mm Hg are observed in the newborn lamb and kid following 147 days gestation (25), and in the newborn human babe after an intrauterine life of twice this duration (196). The rhesus monkey has a mean arterial pressure of about 55 mm Hg at birth after 160 days gestation (71). An increase in arterial pressure during intrauterine life must assist in increasing the umbilical blood flow and the opportunity for exchange between the mother and fetus; however, this is only one means of meeting the increasing demands of growth, and the potentialities of the placental and fetal tissues vary among the species (98).

The course of the rise in arterial blood pressure during intrauterine life is shown in figure 8 for the lamb. It is impossible to assess the relative parts played by alterations in cardiac output and the development of vasomotor tone in contributing to these changes. After about 90 days gestation in the lamb, when the arterial pressure rises more rapidly, the heart rate continues to increase but no cardiac output measurements are available; Barcroft's (25) results in the goat suggest that there may be an increase in cardiac output in relation to body weight from 90 days onward and, as the umbilical blood flow in the lamb decreases in relation to body weight during the same period, the mean body blood flow is probably increased. However, the cardiac output at term is greater per kg of body weight than in the

adult and the low arterial pressure may be accounted for by a low peripheral resistance: as will be seen, this low resistance is probably due to low tonic activity of both nervous and chemical regulating mechanisms.

Pulmonary Artery Pressure

In utero, before the lungs are inflated with air there is no good reason why the pulmonary vascular resistance should be widely different from the vascular resistance elsewhere in the growing fetus. Ardran *et al.* (13) find in the lamb that the pressure in the left pulmonary artery is about 5 mm Hg higher than that in the carotid artery, which suggests that the vascular resistance in the lungs before birth is possibly slightly higher than the combined resistance of the fetal tissues and the placenta; this has recently been confirmed by Assali *et al.* (16). In keeping with these observations are the findings that the thickness of the walls of the two ventricles is approximately the same during development, with a slight preponderance of the right over the left, in the lamb and in the human infant at birth (66).

Development of the Cardiovascular Reflexes and the Responses to Asphyxia and Hormones

The anatomical pathways for the cardiovascular reflexes are laid down early in development in both the human fetus (44) and in the cat (103), but, as predicted by Barcroft, though the machinery is ready it may not be functional and the stage of gestation at which the cardiovascular reflexes are

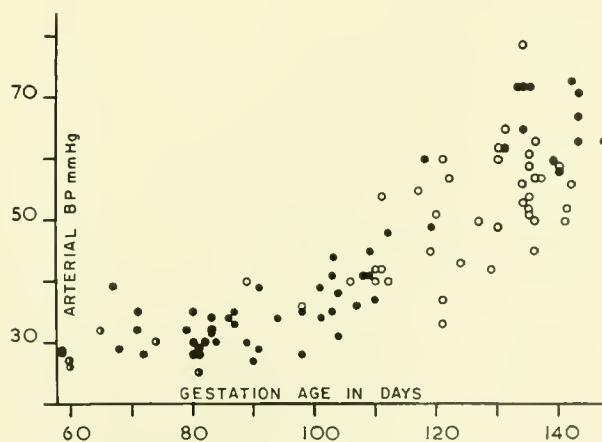


FIG. 8. Systemic blood pressure of fetal lambs, under dialurethane (○) or pentobarbitone (●) anesthesia. [From Dawes (66).]

operative varies among the species. The earlier work is described by Barcroft (25) and the later by Dawes and his colleagues (39, 70, 71, 74).

The responses to asphyxia and to the intravenous administration of hormones have been most generally used to determine the activity of the cardiovascular system in the fetus: the low resistance of the placenta, the low arterial oxygen tension, and the fetal course of the circulation must also influence the final operation of the reflexes. Quantitative data are difficult to obtain when both the peripheral and central mechanisms have not yet reached a steady relationship with each other. However, in the lamb, the steeper rise in arterial pressure which occurs from 90 days onward approximately coincides with the development of increasing responsiveness to asphyxia, as judged by the rise in arterial pressure and heart rate (39); further, the removal of sympathetic tone, following the injection of a ganglion-blocking agent such as hexamethonium causes a greater fall of blood pressure toward term. The tone of the vasomotor mechanisms is probably not fully developed at birth for the mean arterial pressure is about 40 mm Hg lower than in the adult sheep. In the rabbit, cat, and dog, with low arterial pressures at term, the vasomotor mechanisms are probably still less developed at birth (70, 114).

The pattern of the response of the developing cardiovascular system to asphyxia alters with gestational age. The bradycardia which follows either the occlusion of the umbilical cord or the administration of low oxygen tensions to the mother is probably brought about in a variety of ways. In the early fetus of all species cardiac slowing is delayed, it is due to the direct effect of the hypoxia on the pacemaker and is the cause of the ensuing hypotension; this depression of the pacemaker is the final cause of death at any age when hypoxia is prolonged. Later in development, a transient bradycardia of swift onset is observed, which is due to stimulation of the medullary vagal center; later still, this slowing is succeeded by a tachycardia, due to stimulation of the medullary sympathetic center. This response is enhanced by cutting the vagus nerves. The third type of bradycardia is reflex in origin and occurs in response to the rise in blood pressure when vasomotor, baroreceptor, and chemoreceptor activity is developed; the bradycardia seen in the fully developed lamb or human fetus is probably reflex in origin provided the asphyxia is of short duration. It is noteworthy that prolonged asphyxia or hypoxia reduces the heart rate to between 60 to 80 beats per min in most species;

this rate is sustained for varying periods before arrhythmia occurs. Both the tachycardia and the reflex bradycardia during asphyxia may be enhanced by the activity of the adrenal medulla (54). Bradycardia is also the primary response to hypoxic stimulation of the chemoreceptors in the adult animal (60, 61); however, if the brain is also hypoxic, tachycardia usually results from hypoxia of these areas and this tachycardia is enhanced if their oxygen supply is increased.

Quantitative data relating the oxygen saturation of the fetal blood at which the changes in heart rate take place in utero have been provided in the near-term lamb by Born *et al.* (39), and by Reynolds & Paul (161). These observers are not entirely in agreement with each other; both administered nitrogen containing low concentrations of oxygen to the mother under barbiturate anesthesia. Born *et al.* delivered their lambs by Cesarean section and observed an increase in heart rate and blood pressure during the administration of 7.5 to 5.0 per cent oxygen to the mother which caused the fetal carotid arterial oxygen saturation to fall to 50 to 35 per cent; bradycardia did not occur until the arterial oxygen saturation was below 20 per cent for some minutes (fig. 9). Reynolds and Paul's lambs were kept in utero and blood pressures and blood samples were obtained from branches of the umbilical vessels exposed through a small uterine incision. Their results were not so clear cut for fetal tachycardia or bradycardia might be observed following the administration of 13 per cent and 10 per cent oxygen to the mother and 6 per cent oxygen usually caused fetal bradycardia; it is to be noted that the administration of 13 per cent oxygen reduced the arterial oxygen saturation to 30 per cent, a figure which was obtained by Born *et al.* with much lower oxygen mixtures. In the guinea pig, also anesthetized with Nembutal, the administration of 10 per cent oxygen to the mother caused a slight fall in fetal heart rate, during the last third of gestation, while 6 per cent oxygen always caused marked bradycardia (97, 133).

The absence of cardiac acceleration in response to asphyxia early in gestation is not due to the inability of the young heart to increase its rate, for it will respond to adrenaline early in development: in the lamb the heart is more sensitive to adrenaline than are the peripheral vessels for tachycardia occurs at a time when the increase in pressure is relatively small; later the rise in blood pressure is greater and the increase in heart rate diminished, due to the development of baroreceptor reflex activity (74). Acetyl-

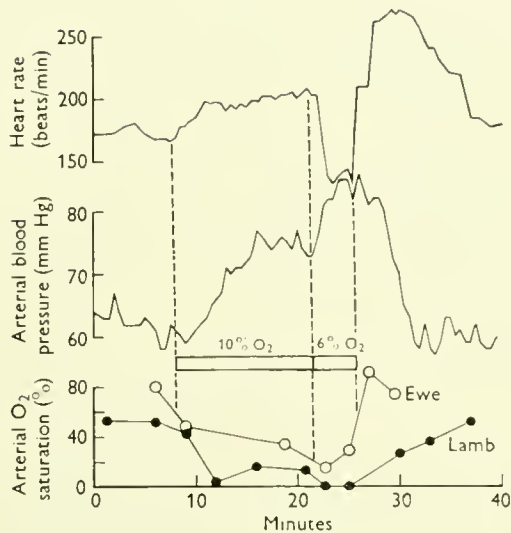


FIG. 9. Response of the fetal heart rate and arterial pressure in the lamb during hypoxia. The rise in blood pressure is accompanied by *a*) tachycardia during the administration of 10% O_2 to the mother, *b*) bradycardia during ventilation with 6% O_2 . [From Born *et al.* (39).]

choline also causes bradycardia and hypotension early in gestation. Dawes and his colleagues consider that the range of effectiveness, per kg of body weight, of those autonomic drugs does not differ from 60 to 160 days in the lamb, and is about the same as in the adult for both the lamb and the fetal rabbit (70, 74). In the lamb at term, with ventilation established, adrenaline and noradrenaline cause a greater rise in blood pressure following occlusion of the umbilical cord, when the low resistance circuit of the placenta is absent. Equal doses of these drugs are also more effective when injected into the femoral vein and pass straight to the left side of the heart and to the coronary circulation, than after injection into the jugular vein when the drug has first to traverse the lungs. Since suprarenal venous blood enters the inferior vena cava, there will be the possibility of a rise in the fetal blood pressure and an increase in the placental blood flow during stress; the effectiveness of sympathomimetic amines liberated during the stress of asphyxia in the fetus may be limited by the reduced responsiveness of the cardiovascular system during asphyxia (195). The adrenal glands and accessory organs contain a pressor substance early in development in the sheep (54) and in the human infant (186). It is also known that sympathomimetic amines are released into the adrenal veins during asphyxia by about 90 days gestation in the sheep; this liberation is due to the direct action of asphyxia on the

adrenal medulla. The splanchnic nerves do not take part in the release until shortly before term. It is perhaps significant that noradrenaline predominates for its pressor activity is the greater and the stimulating action on metabolism apparently more effective than that of adrenaline in the young animal (136).

The catecholamine concentration of human fetal heart, kidney, and lung during the first trimester was found to be roughly similar to that in adult organs though the brain contained much smaller concentrations than in the adult (99); again, norepinephrine predominated suggesting its early appearance at sympathetic nerve endings, but no dopamine was found in any tissue studied. 5-Hydroxytryptamine is found in the blood platelets of the fetal guinea pig two-thirds of the way through gestation and is still lower than the adult at term (174); the brain levels, however, approximate to those of the adult at term (120). The high estrogen and progesterone content of fetal blood (4) may influence both cardiovascular development and the responses of the vessels. The action of many other pharmacological substances on the fetus has been reviewed recently (20).

The importance of cardiovascular regulating mechanisms to the fetus in utero is questionable; asphyxia and hemorrhage are probably the only stresses which the fetus encounters. The responses to hemorrhage have not been frequently studied and Mott suggests that they might possibly be a better indication of the homeostatic capacity of the fetal circulation than the response to asphyxia since the fetus is more resistant to hypoxia than the adult (140).

FETAL PLACENTAL BLOOD FLOW

Effective Perfusion Pressure. Resistance of the Placental Circulation

The effective perfusion pressure across the fetal placental circulation increases as the arterial pressure rises with gestational age. Figure 10 shows some comparative values for umbilical arterial and venous pressure measurements in the lamb (25). Reynolds & Paul (160) have observed umbilical venous pressures as high as 35 mm Hg in the lamb at term; the reason for this rise in umbilical venous pressure may be related to an increased resistance to flow in the fetal liver, through which most of the umbilical blood passes during development. The sphincter of the

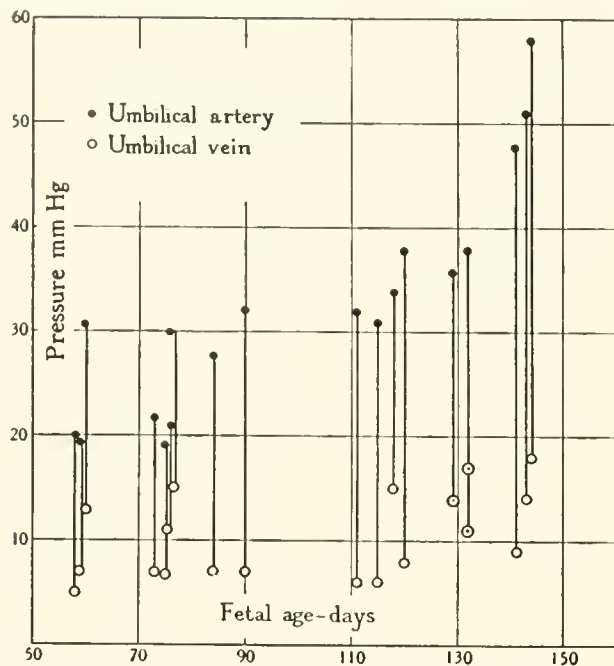


FIG. 10. Pressures in umbilical veins and arteries at successive fetal ages in the lamb. [From Barcroft (25).]

ductus venosus may regulate this pressure and thus both placental and hepatic blood flows in this species.

From figure 10 it can be seen that the pressure drop across the placenta is about 40 mm Hg in the lamb at term and, in comparison, the pressure drop in the systemic circulation is of the order of 60 mm Hg; since about 60 per cent of the cardiac output goes to the placenta the resistance in the fetal placental circulation is about half that of the fetal systemic circulation. The resistance in the fetal liver is still lower than in the placenta for the greater part of the umbilical blood flow traverses this organ with a pressure fall of only 20 mm Hg. No arteriolar regulating mechanism has been described in the chorionic villi but Bøe (37) has demonstrated, in the human placenta, the existence of a shunt mechanism within the villous circulation which may possibly open up during asphyxia and increase the fetal placental reserve. The walls of the capillaries in the chorionic villi have neither smooth muscle nor a nerve supply, but in teased specimens their endothelium has been observed to undergo spontaneous rhythmic movements and to be constricted by histamine and acetylcholine (179).

When the placenta has reached its maximum weight in the lamb, at 80 days gestation, the pressure drop across the placenta is 25 mm Hg; during the last third of intrauterine life this pressure drop only increases by a further 15 mm Hg while the umbilical

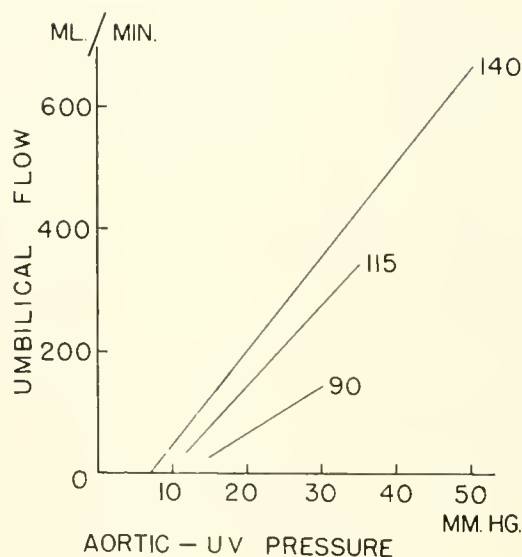


FIG. 11. Pressure flow curves for the fetal placental circulation at 90, 115, and 140 days gestation in the sheep. [From Dawes (69).]

blood flow is increasing tenfold. From pressure-flow measurements in the umbilical circulation (fig. 11) Dawes concludes that the increase in flow is chiefly brought about by a decrease in placental vascular resistance; at the end of term no further decrease in resistance occurs and the increasing flow is dependent on the rising pressure gradient (69).

Umbilical Blood Flow

Umbilical blood flow has been measured in the sheep fetus the most frequently and by a variety of methods. Cooper *et al.* (56) used the venous occlusion plethysmograph (see fig. 12) and found that the blood flow per kg of fetal weight ranged from 250 ml per min at 60 days gestation to about 130 ml per min at term, 147 days. The actual flows and their decrease in relation to body weight are in good agreement with the later observations of Acheson *et al.* (1) using the same technique but a different breed of sheep (fig. 13). Reynolds *et al.* (158) made a few measurements of the blood flow in the umbilical artery in the lamb by cineangiography and concluded that there was no reduction in relation to body weight at the end of term; this suggests that the fall in blood flow using the plethysmograph may be an artifact due to the greater sensitivity of the umbilical vessels at this time. In the guinea pig the venous occlusion plethysmograph gave values of 45 to 108 ml per kg per min, with no tendency to change as the fetal weight increased (172): the arterial pressure is lower

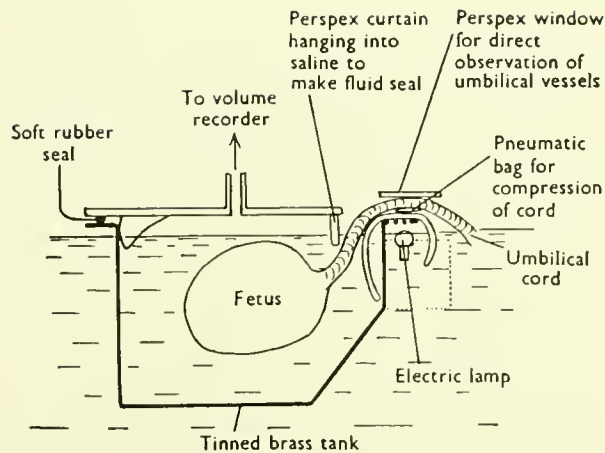


FIG. 12. Section through a fetal plethysmograph at the point of entry of the umbilical cord. The umbilical cord lies on a gently curved perspex strip. [From A. D. M. Greenfield. A foetal plethysmograph. *J. Physiol., London* 108: 158 (Fig. 2), 1949.]

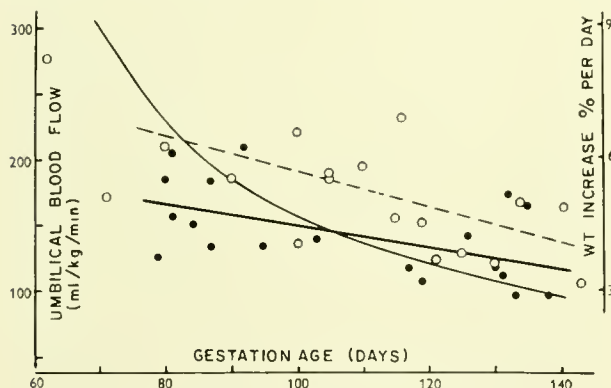


FIG. 13. Umbilical blood flow in the lamb, per kg body weight during gestation. [Data of K. E. Cooper *et al.* (○—) G. H. Acheson *et al.* (●—).] The thin continuous curved line indicates the weight increase per cent per day. [From Acheson *et al.* (1).]

than in the sheep and the pressure gradient between artery and vein is likely to be smaller and, assuming that the vascular resistances are similar, this will account for the lower placental blood flow. When these umbilical blood flow rates are compared with growth curves it is observed that 5.5 liters of blood are required to lay down 1.0 g of fetal tissue in the sheep, as compared with only 1.3 liters in the guinea pig, (98). Using an electromagnetic flowmeter Assali *et al.* (17) found the umbilical arterial flow in nine human fetuses of 12 to 28 weeks gestation to range between 94 and 127 ml per kg per min. It is remarkable that vessels so contractile as those in the cord have yielded, on the whole, reproducible results. Each worker has been most aware of the experimen-

tal errors involved in his measurements. Dawes & Mott (72) also point out that the venous occlusion plethysmograph has a disadvantage in the present application, for when the umbilical vein is temporarily occluded the return to the heart must be reduced; they found that a velodyne flowmeter, providing a direct measure of flow, inserted into the vein in the abdomen gave results which were higher than those obtained by the plethysmograph.

The umbilical blood flow may be increased at the end of term in the lamb by reducing the fetal arterial oxygen saturation (39). This is probably mainly due to the rise in arterial pressure caused by the response of the fetal vasomotor center to the altered chemical composition of the blood. Reynolds & Paul (160) found that no rise in umbilical venous pressure accompanied the rise in umbilical arterial pressure and suggested that the tone of sphincter of the ductus venosus was decreased in response to the increased umbilical venous flow. The injection of adrenaline into the femoral or jugular vein of the fetus causes an increase of umbilical blood flow which is proportional to the rise in arterial blood pressure (74) (fig. 14). Isolated umbilical vessels are very sensitive to the vasoconstrictor action of adrenaline and these results suggest that the hormone is destroyed before it reaches the umbilical vessels; no figures are available to show how the hormone influences the resistance in the placenta. The umbilical blood flow is reduced

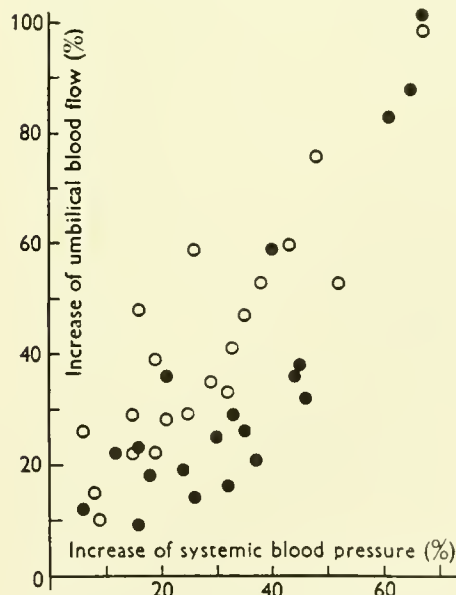


FIG. 14. Increase in umbilical blood flow following the injection of adrenaline (●) or noradrenaline (○) in the mature fetal lamb. [From Dawes *et al.* (74).]

when the arterial pressure falls following the injection of hypotensive drugs such as acetylcholine and hexamethonium into the fetal circulation (74) and following severe hypoxaemia of 10 to 15 min duration (69).

Oxygen Requirements and Environment of the Fetus

Primarily dependent upon the maternal placental circulation, the fetal heart provides an umbilical blood flow which, under normal conditions, maintains a steady oxygen consumption of 4 to 6 ml per kg body weight per min in both the lamb during the last half of gestation (1) and in the human fetus of 9 to 28 weeks gestation (17): this represents an oxygen consumption in relation to weight comparable with the adult and the constancy is remarkable in view of the changing oxygen utilization of the various organs, and their varying weights in relation to each other, during development. Huckabee *et al.* (111) point out that without a knowledge of the anaerobic metabolism of the fetus it is impossible to obtain an accurate estimate of the energy requirements of growth from the quantity of oxygen consumed alone; however, there is no good evidence for anaerobic metabolism in the normal fetus for blood lactate levels are comparable with the adult (71). Huckabee *et al.* also point out that the metabolic rate of the fetus, if it were known, is not synonymous with the metabolic rate required for the life and growth of the fetus and the metabolic needs of the placenta must be included. These observers found in the goat, as did Assali *et al.* (17) in the human, that the oxygen consumption of the pregnant uterus was about 10 ml per kg per min; the calculations were made from uterine blood flow and A-V O_2 differences. But, while Assali *et al.* consider the placenta to have a greater oxygen consumption than the fetal tissues, Huckabee *et al.*, from uterine oxygen utilization measurements after fetal death, suggest that this may be the reverse; the latter estimate of fetal oxygen consumption, as approximately 10 ml per kg per min, would agree with determinations of the minimal oxygen consumption of the newborn lamb. However, Dawes and Mott have shown that such a high oxygen consumption is characteristic of the newborn only and is attained at different ages in the different species; further, they have demonstrated that this increase in oxygen consumption is not dependent upon the raised arterial oxygen saturation following the establishment of respiration for it does not occur in immature lambs

delivered by Cesarean section and artificially ventilated (72).

What is the oxygen environment of the fetal tissues in utero? Recently, Misrahy *et al.* (135) have measured the oxygen availability (aO_2) in fetal brain and kidney, in a number of species under Nembutal anesthesia. Nondiffusion limited polarographic electrodes, 100 μ in diameter, with a circumferential recording surface, 2 mm in width, were inserted into the tissues, with little disturbance of the uterine wall; the aO_2 ranged between 18 per cent and 30 per cent of the diffusion current in air, corresponding to 30 to 45 mm Hg O_2 and was similar to the maternal tissue oxygen tensions measured in the same manner. Misrahy *et al.* consider these readings to represent the rate of oxygen transport between the capillaries and the active cells. The tension of oxygen in the arterial blood of the fetus is, however, probably considerably lower than that in the maternal blood. It is difficult to assess the values for arterial oxygen saturation in utero for when the uterus is opened and umbilical vein samples collected the placental circulation is impaired to an unknown extent. Westin (187) has shown, by hysterophotography, that the oxygen saturation of the fetal blood is probably high in 14 to 18 week human fetuses for the skin is pink and the umbilical vein arterial in color in utero, and Dawes and his colleagues (1, 39) have observed arterial oxygen saturations as high as 74 per cent in the lamb near term. In the human at term, blood collected from the choriodecidual space by placental puncture has been reported to have a mean pO_2 of 38 mm Hg; the pO_2 in umbilical vein blood is probably 10 mm lower (31). These results in the human should, however, be regarded with reserve for there is no means of knowing whether the sample of blood obtained comes from the choriodecidual space or a uterine vein.

How is equality of oxygen availability to the fetal and adult tissues attained in spite of the low arterial oxygen saturation in the former? The mechanisms appear to be, for the most part, similar to the adult response to low arterial oxygen saturations. First, the fetal blood has a greater affinity for oxygen than the maternal blood; this is a property of the fetal hemoglobin and its environment in the red cells which enables fetal blood to leave the placenta with a greater oxygen saturation than the maternal blood at low oxygen tensions. The factors involved in the transfer of O_2 and CO_2 between the maternal and fetal circulations are clearly outlined by Barron & Meschia (30) and Bartels *et al.* (31). Second, there is a

steady rise in the blood hemoglobin in fetuses of all species during gestation. Most are born with levels which are higher than that of the mother (29) and erythropoietic concentration is known to be high in the cord blood of many species (6, 41). Third, the average blood flow through the fetal tissues is high. This has not been compared with the adult values for each individual tissue but estimates of the fetal cardiac output in the lamb are high, as already described and amount to an average tissue flow of about 120 ml per kg per min, which is at least twice the flow in the adult sheep. These cardiac output measurements have been calculated indirectly from umbilical blood flow measurements and the distribution of blood within the fetus with an open chest and are, therefore, probably an underestimate. Approximate calculations for the human fetus also suggest that the average body blood flow is high.

INFLUENCE OF HYPOXIA AND ASPHYXIA ON THE FETUS

The effects of a prolonged reduction in oxygen supply have been observed in fetuses born to mothers at high altitude and the possibility of hypoxia as a cause of congenital malformation has already been discussed: experimentally the influence of acute hypoxia, produced by maternal breathing of low-oxygen gas mixtures has been studied the most frequently. The results of true asphyxia may be observed during marked impairment of the maternal placental circulation or the mechanical obstruction of the umbilical vessels.

Hemoglobin

The possibility of a rise in blood hemoglobin concentration, in response to a reduced oxygen supply, first attracted the attention of Joseph Barcroft (25) who correlated the fetal hemoglobin level with the percentage saturation of the umbilical vein blood with oxygen, in the lamb at term. This idea has proved most controversial clinically (118, 182), particularly because subsequent investigators did not heed Barcroft's warning concerning the difficulties of collecting a good specimen of umbilical vein blood, and his awareness of the variety of conditions which might bring about rapid changes in the oxygen saturation of cord blood. Neither the oxygen saturation of the blood in the umbilical vessels at birth, nor the total level of hemoglobin in the blood and the relative proportion of fetal hemoglobin, contributing

to this, have proved to assist in the interpretation of either the extent or duration of any impairment of the intrauterine environment. However, it is now certain that fetal hemopoietic tissues can respond when oxygen availability is reduced for the young born to llamas at 15,000 ft have higher blood hemoglobin concentrations than those born at sea level (150). It is interesting to speculate on this response at altitude in the fetus: as described, erythropoietic concentration is high in cord blood at sea level and may represent the fetal response to low arterial oxygen tensions despite the adequate availability of oxygen to the majority of fetal tissues; adult hemopoietic tissue, however, will also respond at 25,700 ft (7,830 m) when the arterial oxygen tension is reduced to 33 mm Hg (151), a value which is normal for the fetus. Born *et al.* have shown that fetal hemoglobin concentrations increase during acute hypoxia in the lamb, which suggests that red cells may have been released from the spleen or there may only have been a loss of plasma to the extracellular space (39).

Blood Flow

It is doubtful if the possibility of increasing the tissue and placental blood flow in response to a reduction in oxygen supply is significant in the fetus: in the lamb, younger than 60 days of gestational age, both umbilical and tissue blood flows will probably fall since there are no reflex mechanisms to elevate the blood pressure and the depleted oxygen supply will cause bradycardia. Later, when the cardiovascular reflexes begin to be developed, a rise in arterial pressure and carotid and umbilical blood flow is observed in response to asphyxia or low oxygen tensions; these responses occur when the fetal arterial oxygen saturation is reduced to 50 to 35 per cent, following the administration of 7.5 to 5.0 per cent oxygen in nitrogen to the mother (39). The increase in carotid and umbilical blood flows probably occurs at the expense of the blood supply to the major portion of the body, for it is unlikely that the cardiac output increases: there is no experimental evidence to support this statement, but it is known that hypoxia does not increase the cardiac output in the newborn lamb (57); this lack of response is possibly related to the very high cardiac output at this time, for the fetal cardiac output at term is at least twice that of the adult per kg body weight. The decrease in oxygen consumption of the hind quarters in the lamb during hypoxia may be evidence for peripheral vasoconstriction.

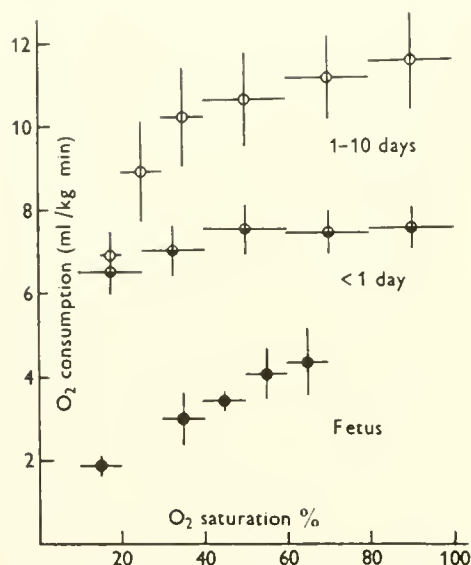


FIG. 15. Oxygen consumption per kilogram body weight at different arterial oxygen saturations. (●) Fetal lambs; (◐) lambs less than 1 day old; (○) lambs 1–10 days old after the rise in minimal oxygen consumption (95% confidence limits are shown); horizontal lines indicate the range of observations. [From Cross *et al.* (57).]

Oxygen Consumption

The fetus has a third mechanism of defense at low oxygen tensions, that of lowering its oxygen consumption. Cross *et al.* have shown that this occurs when the umbilical arterial oxygen falls to 50 per cent saturation in the lamb, and the effect increases as the arterial oxygen tension is reduced still further (57) (fig. 15). The fall in oxygen utilization may be due primarily to the decrease in blood flow to the majority of tissues, as discussed above, for it is accompanied by an accumulation of lactic acid and depletion of tissue glycogen stores (171). It would be interesting to know if the tissue temperature falls as it does in the adult when the blood flow and oxygen supply are reduced to muscle (169). A reduction in oxygen consumption with low arterial oxygen tensions is not readily demonstrated in the adult animal, for the cardiac output increases and the heart is liable to sudden failure before low oxygen tensions are reached (1). The inability of the fetal cardiac output to increase, and the capacity of the heart to continue to beat during asphyxia, must be important for survival during birth.

The oxygen consumption of newborn animals, at their neutral temperature, increases after birth at intervals which vary with the species (67, 72). In the lamb, the minimal oxygen utilization is trebled

within 24 hours of delivery to correspond with the metabolic requirements of its surface area, and usually no shivering occurs (72); this recently acquired increase in oxygen consumption is not well maintained when the arterial oxygen saturation is lowered. Hill has also observed that the increase in oxygen consumption without shivering, in response to a low environmental temperature, is particularly susceptible to hypoxia (107).

Heart Rate During Reduction in Maternal Placental Blood Flow

The influence of asphyxia on the fetal heart rate in utero and its relationship to the degree of reduction in maternal placental blood flow, or the short-term placental reserve, has important practical applications. The physiology of the response of the fetal cardiovascular system to asphyxia has already been discussed. It is generally agreed that tachycardia is the first indication of intrauterine asphyxia at term in the human infant (108), and in the lamb. Born *et al.* observed that tachycardia did not occur in the lamb until the umbilical arterial oxygen saturation was reduced to 50 to 35 per cent, during the administration of 7.0 to 5.5 per cent oxygen to the maternal sheep; bradycardia, most usually associated with intrauterine asphyxia, was not observed until the oxygen saturation reached 20 per cent (39). The influence of the accumulation of carbon dioxide, occurring in asphyxia, is not known. The time course of both the cardiac acceleration and slowing observed experimentally and clinically is very variable, depending upon the rate of onset and degree of asphyxia induced, the existing oxygen environment and the previous asphyxial history. For instance, a sustained acceleration is readily observed as the tension of oxygen administered to the maternal animal is gradually lowered, but it is only transient when nitrogen is inspired by the mother or when the cord is tied; frequently acceleration does not precede the bradycardia in the latter circumstances. Hon (108) has described two time courses for fetal bradycardia in the human infant during labor: the one, which he describes as physiological, occurs following a uterine contraction and most usually in vertex presentations; the heart slows briefly and recovers swiftly within 15 sec. The second, which Hon calls pathological, has a longer time course and is considered to be possible evidence of previous asphyxia or a permanent reduction in uterine blood flow. An example of the influence of limiting the

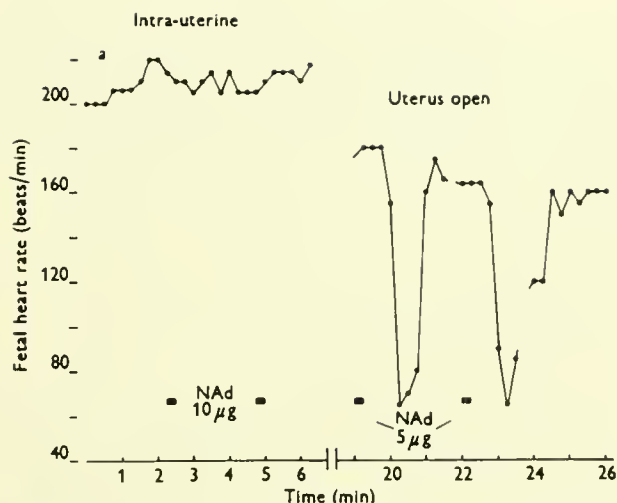


FIG. 16. In the guinea pig, of 54 days gestation, *a*) the fetal heart slows when the uterus is opened; *b*) marked fetal bradycardia occurs following the maternal injection of noradrenaline only after the uterine wall is opened. [From Martin & Young (133).]

blood supply to the fetus upon the susceptibility to further asphyxia as shown in figure 16; after the uterine wall was opened, to expose the fetus, the uterine muscle contracted away from the incision around the uterine blood vessels, and cardiac slowing could be produced with a smaller dose of vasoconstrictor substance in the maternal circulation than when the fetus was in utero.

Reduction in the uterine blood flow giving rise to these various patterns of fetal heart rate changes may be brought about in many ways. It follows the injection of either hypotensive (82, 194) or vasoconstrictor (34) drugs into the maternal circulation; the effect will be reversible or not according to the dose given and the duration of action of the pharmacological substance. Uterine blood flow may be markedly reduced temporarily, by adrenaline or noradrenaline in the maternal circulation, and this may be one reason for the poor placental transfer of noradrenaline which has been observed (168). In the guinea pig the uterine blood vessels become sensitized to the action of adrenaline as gestation proceeds and following the administration of both estrogen and progesterone (133). It is possible that there is a reduction in maternal placental blood flow before conversion of the uterus from the spherical to oval shape (154, 157).

The influence of uterine contraction on the fetal heart rate has been most extensively studied and depends upon the duration of the contraction, its frequency and upon the intrauterine pressure developed (7, 15, 109). It is probable that the first effect of any

uterine contraction will be to upset the functional countercurrent mechanism which enables the maternal arterial blood in the intervillous space to reach the base of the chorionic villi and enable final arterialization of the umbilical venous blood. Hendricks *et al.* (104) have made simultaneous recordings of the intra-amniotic and intervillous pressures in the human and consider the sequence of events on the maternal side of the placenta to be complicated before the oxygen supply to the fetus is impaired during a contraction. They observed the pressures in the intervillous pool and the amniotic cavity to be about equal, both when the uterus was relaxed and during systole; the increase in the intervillous pressure lagged behind the intra-amniotic pressure rise during contraction. It is suggested that the intervillous volume is slightly reduced during the early phase of contraction; but once the intra-amniotic pressure exceeds that in the uterine vein, venous drainage will cease and the intervillous volume become expanded as the arterial inflow continues. The oxygen supply, though slowed, may continue for a considerable time during contraction, and the spongy structure of the placenta and the large venous sinuses allows local pressure differences to be distributed and prevent retroplacental hemorrhage. The increased pressure in the intervillous space will be transmitted to the fetal vessels and, added to a reduced oxygen supply, there will be a reduction in umbilical blood flow as the resistance increases. Reynolds & Paul (159) observed in the lamb, in utero, that rhythmic contractions of low intensity which caused a rise of intra-amniotic pressure of about 5 mm Hg caused an equal rise in fetal blood pressure but no change in heart rate: manual pressure on the uterus or the application of weights, from 1 kg upward, caused a rise of arterial pressure in the fetus which exceeded the rise in amniotic pressure; this was asphyxial in origin and accompanied by bradycardia. Strong contractions induced by Pitocin, which raised the intra-amniotic pressure more than 10 mm Hg, gave similar vascular responses in the fetus (15, 159).

The quantitative relationship between reduction in maternal placental blood flow and the appearance of fetal bradycardia has been supplied in the sheep by Adams *et al.* (2); no change in fetal heart rate was observed until the uterine blood flow, measured with an electromagnetic flowmeter, was reduced to about one-third of the control level following the injection of adrenaline into the maternal circulation. This relationship was readily predicted from the heart rate changes occurring during the administration of

low oxygen tension mixtures to the mother in both the sheep and the guinea pig (39, 133). It appears that there is no species difference for the sensitivity of the fetal heart to hypoxia in utero. Hon has also described intermittent fetal bradycardia during delivery which he considered to be unrelated to alteration in placental blood flow and due to either compression of the cord (109) or medullary asphyxia. The bradycardia during cord compression had a long time course, but swift physiological bradycardia was frequently observed in vertex presentations and could be related to the degree of cervical dilatation and was possibly caused by the rise in intracranial pressure. This is an old clinical observation and Harvey Cushing also observed bradycardia in adult animals during experimental asphyxia of the medulla (59).

The great ability of the fetus to survive asphyxia is still not understood (139, 171) and it is not known whether the ultimate damage to the tissues is mainly due to the absence of oxygen and, therefore, the supply of energy, or to the fall in pH as the lactic acid accumulates. Whittam (188) has shown that anoxic fetal kidney slices maintain their potassium content better than adult tissue and, if this is true for both the heart and the brain, it possibly explains the maintenance of their excitability and activity for long periods during asphyxia. Mott stresses the importance of the maintenance of a circulation during anoxia so that glucose, from the liver glycogen, may be supplied to all the tissues, and lactic acid removed (139): liver glycogen is partially mobilized during anoxia and the brain and heart both suffer a large reduction in glycogen content; in the young fetus total lactate production can be accounted for by the

loss of carbohydrate from the heart. The survival time of the fetal heart is directly related to its carbohydrate stores which are larger than those of the adult (fig. 17); these reserves may be depleted by repeated episodes of hypoxia which may have a cumulative effect.

CHANGES IN THE FETAL CIRCULATION AT BIRTH AND IN THE NEONATAL PERIOD

Umbilical Cord; Ductus Venosus

The detailed structure of the umbilical cord varies widely among the species, but all the arteries and veins have thick muscular walls and lack a nerve supply (27); the horse and rabbit have separate sphincters in the region of the umbilical ring (194). The isolated umbilical and placental vessels are very reactive: constriction occurs in response to cooling, stretching, or handling, the presence of the sympathetic autonomic drugs in the perfusion fluid and high oxygen tensions; relaxation occurs in the presence of low oxygen tensions and high CO₂ tensions. Rogers (163) observed the phenomenon of "pressure spasm," a complete but temporary occlusion following an increased and sustained perfusion pressure; this response to pressure is also observed in denervated systemic vessels (33). Following a natural birth there will, therefore, be many factors combining to ensure an effective closure of the umbilical vessels. Intrauterine asphyxia might be expected to impair the effectiveness of these stimuli and, recently, it has been observed that the cord continues to pulsate for long periods in infants following a difficult delivery (80).

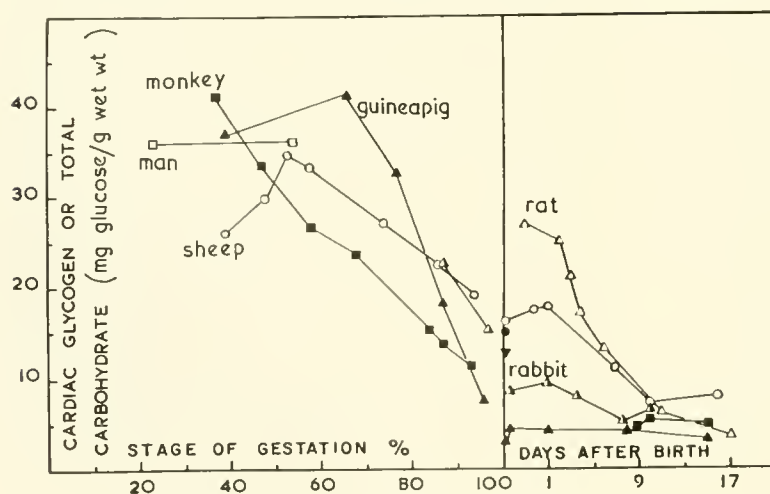


FIG. 17. Cardiac glycogen in different species before and after birth. [From Shelley (171).]

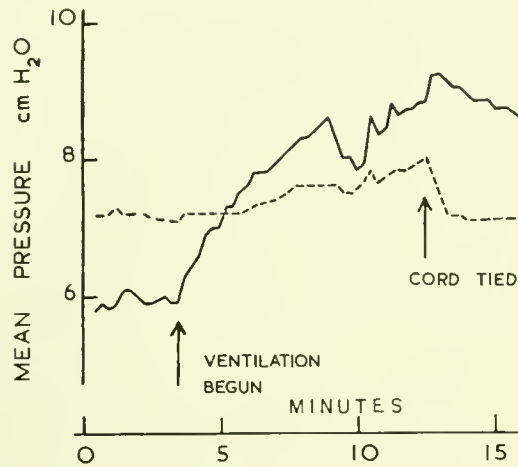


FIG. 18. Ventilation of the lungs of a mature fetal lamb caused the mean left atrial pressure to rise above the pressure in the inferior vena cava (IVC); occlusion of the umbilical cord caused the IVC pressure to fall. Both, therefore, contribute to the rapid reversal of the pressure gradient across the foramen ovale, resulting in its closure after birth. (Modified from G. S. Dawes. Changes in the circulation at birth. *Brit. Med. Bull.* 17: 152, 1961.)

The mechanism for the functional closure of the ductus venosus is unknown but it is important that this should take place early in neonatal life. The formation of an Eck fistula, with the portal blood short-circuiting the liver, passing through the portal sinus and straight into the inferior vena cava, might explain the hypoglycemia and icterus which sometimes occurs in the neonatal period, especially in premature infants. Cardiac catheterization through the umbilical vein depends upon anatomical patency of the ductus venosus; there is evidence that it is either closed or absent in about 30 per cent of newborn infants (167). However, when the ductus venosus is patent it may be visualized by radiopaque substances up to 12 days after birth (146).

Fetal Channels in the Thorax

The first breath initiates the changes in course of the blood streams in the heart: expansion of the lungs decreases the resistance in the small vessels and the resulting increase in pulmonary blood flow raises the left atrial pressure above that in the inferior vena cava, closing the foramen ovale functionally (fig. 18); this closure is assisted by the fall in the inferior vena caval pressure due to the temporarily reduced venous return to the heart, following occlusion of the umbilical vessels. The whole volume of inferior caval blood now joins the superior caval blood in the right

atrium to maintain the high pulmonary blood flow. As a result of the reduced pulmonary vascular resistance the pulmonary arterial pressure falls below the systemic level and blood flow through the ductus arteriosus is diminished.

The radiological studies in the sheep and the human infant (26, 129), at first suggested that when respiration is off to a flying start the functional closure of both the foramen ovale and the ductus arteriosus is immediate. However, anatomical closure is not complete for some weeks and there is evidence that blood may flow through both these channels, probably intermittently, for about a fortnight after birth; this is demonstrated in the angiocardigraphic studies and in dye dilution curves which, in normal babies, are characteristic of pathological states with a patent ductus (149). More direct evidence for a patent ductus with a left-to-right shunt has been obtained in mongol (117) and in normal infants (3); during cardiac catheterization it was found that blood obtained from the pulmonary artery contained more oxygen than that collected from the right auricle and, in addition, the pulmonary arterial pressures were higher than expected. Dawes and his colleagues have measured this flow in the lamb and find it considerable (76). Blood flowing through the wide open ductus arteriosus creates no murmurs, but as the vessel constricts there is turbulence of the swiftly flowing stream and murmurs attributed to this can be heard in both the sheep (76) and the human infant (50). The direction of this shunt may be from left to right or right to left according to the relative pressures in the pulmonary and aortic trunks. Following expansion of the lungs, the pulmonary arterial pressure falls relative to the systemic pressure and there is the possibility of a left-to-right shunt; if this occurs, the work of the left heart will be increased but, during recirculation of the blood through the lungs, there is a further opportunity for oxygen uptake which is advantageous when the ventilation is poor. During asphyxia or crying the pulmonary arterial pressure rises and may exceed the systemic pressure causing the possibility of a right-to-left flow again, when the lower half of the body will probably receive blood of a lower oxygen content than the upper half (88).

The wall of the ductus arteriosus has a sphincter-like structure and the musculature a poor nerve supply. In the lamb fetus the lumen is nearly as large as the pulmonary artery and descending aorta and the blood flow through it approximately one-third of the combined output of the two ventricles (76);

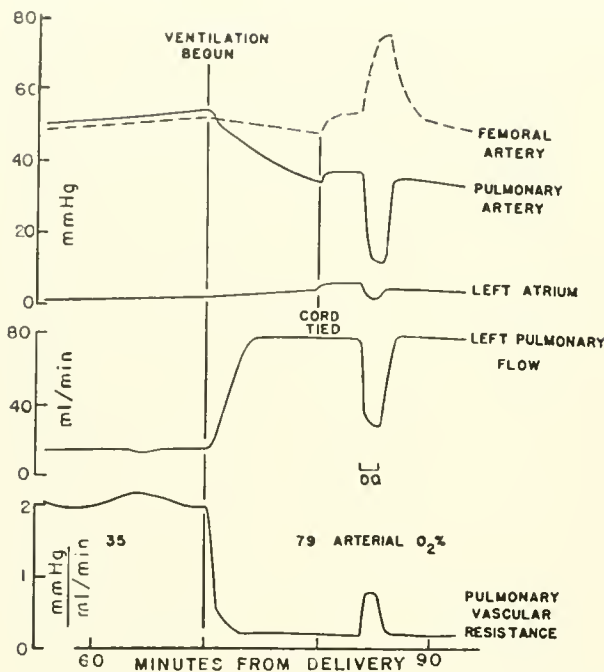


FIG. 19. Changes in the circulation on ventilating the fetal lung: a) artificial positive pressure ventilation of the lungs caused a large fall of pulmonary vascular resistance, an increase in pulmonary flow and a fall in pulmonary artery pressure. b) Temporary occlusion of the ductus arteriosus caused a rise in femoral pressure and a fall in pulmonary pressure and flow, showing that blood had been flowing from the aorta into the pulmonary trunk. The figures 35 and 79 indicate the carotid arterial $O_2\%$ saturation. (From G. S. Dawes. Changes in the circulation at birth. *Brit. Med. Bull.* 17: 151, 1961.)

with the reduction in pulmonary arterial pressure the flow is diminished and the wall constricts. Closure of the ductus is not dependent upon its nervous connections and will occur following inflation of the lungs provided the oxygen tension is high and, like the umbilical vessels, it will dilate when the blood oxygen tension is low (27, 40); constriction can, however, occur during asphyxia and this may be due to the release of sympathetic amines. The responses of the ductus arteriosus and the cord vessels are common to all unstriated muscle, and the exemption of the neighboring aorta and pulmonary artery is due to the preponderance of elastic fibers in the tunica media of the latter vessels.

In the fetal lamb in utero the right atrial pressure is 1 to $1\frac{1}{2}$ cm H_2O higher than the left atrial pressure (fig. 18). This pressure difference occurs because the pulmonary venous return to the left auricle is small and only about one-ninth of that returning to the right side of the heart; 75 per cent of the inferior caval blood is directed by the valve of the foramen

ovale and redistributes the venous return to maintain the left ventricular output and systemic and placental blood flows. Following inflation of the lungs the decrease in pulmonary vascular resistance enables the pulmonary blood flow to treble and as the interatrial pressure difference is reversed the foramen ovale closes (77); Dawes and his colleagues consider that clamping the cord before the first breath, thus reducing temporarily the inferior caval flow, might be sufficient to lower the right atrial pressure and assist closure of the foramen ovale. However, maintenance of its closure will depend upon the increased pulmonary venous return. In small animals the preponderance of left-over-right atrial pressure is difficult to demonstrate within the first 24 hours of birth, but develops during the subsequent days and weeks; the maintenance of this pressure difference which is observed throughout life is probably the combined influence of filling and elasticity of the two ventricles.

Pulmonary Vascular Resistance, Arterial Pressure, and Blood Flow

The way in which the first breath initiates the reduction in pulmonary vascular resistance is not yet fully explained. Using a density flowmeter, Dawes *et al.* measured the blood flow in the left pulmonary artery of lambs delivered by Cesarean section; following positive pressure ventilation with air, oxygen, or nitrogen they observed a three- to fourfold increase in pulmonary blood flow, a decrease in arterial pressure and calculated a tenfold decrease in pulmonary vascular resistance (13, 78). Distention of the lungs with warm saline was not found to increase the pulmonary blood flow and no change in circulatory pattern probably takes place during respiratory effects in utero when amniotic fluid is known to enter the lungs (65). Dawes' conclusion that the decrease in pulmonary vascular resistance was primarily due to the mechanical factors associated with ventilation was questioned, recently, by Cook *et al.* (55) following observations in newborn lamb preparations in which the two lungs were ventilated separately and the pulmonary vessels perfused at a constant pressure; alveolar hypoxia and hypercapnia caused vasoconstriction in the pulmonary circulation which was more marked than that observed in the adult lung (84) and ventilation with nitrogen alone gave variable results—possibly on account of differences in local CO_2 tension. Recent observations have shown that both an increase in arterial and alveolar pO_2 and a reduction in pCO_2 contribute toward the increase in

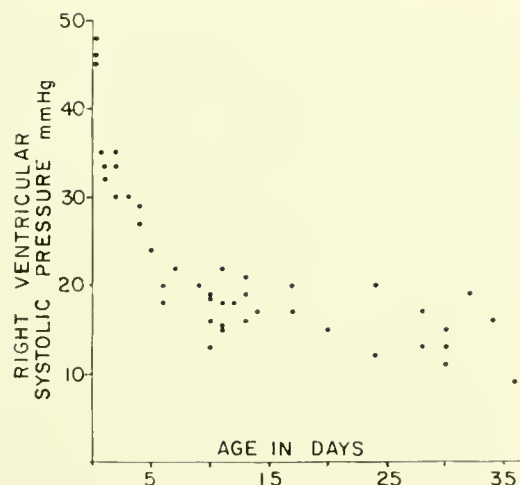


FIG. 20. Right ventricular systolic pressure in 15 puppies during the first 5 weeks of neonatal life. [From Rudolph *et al.* (166).]

pulmonary blood flow at the onset of pulmonary ventilation in the lamb; similar changes in blood chemistry, and vasodilator drugs, also increase blood flow in the unexpanded fetal lung (73) which would suggest that a decrease in vascular resistance is not necessarily due to uncoiling of vessels as suggested by Reynolds (156). Once started, the increase in blood flow itself together with the raised left atrial blood pressure may help to maintain a low pulmonary vascular resistance as it does in the adult lung (42). Pulmonary vascular resistance has been calculated in the human infant at birth and during the first 3 weeks of life from measurements of the pulmonary artery pressure and cardiac output, determined by the Fick principle (164). Within a few hours of delivery the pulmonary vascular resistance is about 550 dynes per sec per cm^{-5} in comparison with an assumed fetal value of 8,000 dynes sec cm^{-5} . This neonatal value is still considerably higher than that found in the older infant and the adult, but is already much less than the systemic vascular resistance; it declines to the adult level by 6 months of age by which time the walls of the pulmonary arterioles are reduced in thickness (62). The lung blood volume does not change immediately following this large drop in resistance (66) but a considerable increase has been demonstrated within the first 24 hours of life in the guinea pig (92).

The pulmonary arterial pressure is reduced by about a half to approximately 35 mm Hg during the immediate postnatal period in both the lamb and the human infant, and in the puppy (165, 166). The final reduction in pressure occurs gradually over

the following weeks (fig. 20). The thickness of the walls of the two ventricles is nearly equal in the fetus with a slight preponderance of the right chamber; while the pulmonary vascular resistance and arterial pressure are falling and the systemic vascular resistance and pressure are rising in the newborn period, the right ventricular wall decreases in thickness and the left ventricular wall increases in thickness; in the human infant these changes are nearly completed within the first month of life (121).

The Heart

The immediate changes in heart rate in the human infant following a normal birth are variable and transient (173). In the lamb delivered by Cesarean section the heart rate slows when the cord is clamped (66): this may be reflex in origin for the arterial pressure is raised, but may also be due to the direct effect of asphyxia on the pacemaker; the bradycardia is followed by tachycardia once respiration and oxygenation of the blood are established. During the first 2 days after birth the heart rate of the human infant is usually lower than in utero, about 120 beats per min, and rises during the first week of life (14, 21, 198). The temporary bradycardia is possibly the combined effect of the low body temperature during this period (52) and the residual effect of perinatal asphyxia. In the newborn kitten and puppy the heart rate varies widely, ranging from 180 to 260 per min during the first 15 weeks of life (114). The heart rate of the newborn monkey is 205 ± 20 (SD) beats per min (116).

The heart volume has been measured radiologically in the human infant (124) and found to have an average value of 48 ml in 55 infants on the day of birth; during the first hour of life there was an increase in volume with a return to the immediate postnatal level within 3 hours. During the subsequent 4 days of life the volume diminished by 25 per cent and thereafter increased; the decrease in heart size was more pronounced in premature babies. These early changes in heart volume and the enlargement of the heart which occurs following birth asphyxia (51) need to be made simultaneously with other circulatory measurements, for a better understanding of the events taking place.

Cardiac output measurements in newborn human infants by the dye dilution technique (149) and using the Fick principle (3) provide a very wide range of values 180 to 850 ml per min, which is probably explained by the patency of the fetal channels; this is a

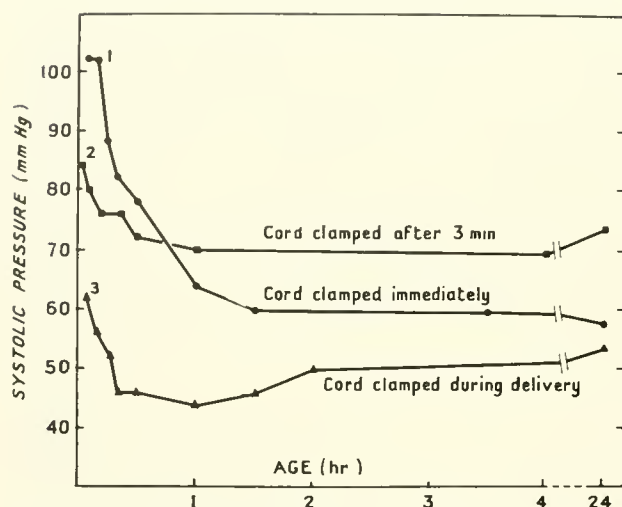


FIG. 21. Three representative records of the changes in the systolic pressure of normal babies during the first 24 hours of life. [From Ashworth & Neligan (14).]

factor which must influence all but the cardiometer results in animals, which also have their inherent disadvantages. The average cardiac output of the human infant, 540 ml per min, corresponds to a value of 180 ml per kg per min and is about double the value in the adult per kg body weight; the cardiac index is 2.5 liters per min per m^2 . Assuming a newborn heart rate of 140 per min, the stroke volume will be approximately 4 ml. It may be noted that if the estimates of cardiac output in utero are correct, 200 ml per kg per min (17), the value does not change in the neonatal period and no increase in oxygen consumption is observed (58). On the other hand, there is evidence for an increase in cardiac output following birth in the lamb: Cross *et al.* (57) made calculations using the Fick principle and obtained values of 325 ± 30 ml per kg per min, which compared with the near term intrauterine estimate of 235 ml per kg per min for both ventricles; a single ventricle has therefore increased its output three-fold. This increase may be the response to the raised oxygen consumption which occurs in the lamb at birth or it may be the expression of the better measurements which are possible after birth.

Systemic Pressure, Cardiovascular Reflexes and Peripheral Resistance

When the changes in systemic arterial pressure at delivery are measured, a discrepancy exists between the lamb and the human baby; namely, a small transient rise of pressure is observed following the

initiation of ventilation or occlusion of the cord in the lamb (66) while, remarkably, in the human infant no change of pressure is seen (183, 196). There are many possible explanations for this difference: first, the different types of maternal placental circulation; second, the influence of contraction of the uterine muscle on this circulation; and third, the alteration of distribution of blood between the placenta and fetus before the arterial measurements are made. The arterial pressure measurements in lambs have all been made on fetuses delivered by Cesarean section and, as the sheep uterus is not very reactive to surgery, the maternal and consequently the fetal placental circulations are probably not greatly impaired. When the lamb is delivered vaginally the maternal placental blood flow is not reduced during labor and does not decrease until separation of the placenta some hours after delivery of the fetus (15). The temporary rise in pressure observed is therefore probably due to the removal of the low resistance circuit of the placenta, and a small rise in arterial pressure following cord occlusion has also been observed in the rhesus monkey delivered by Cesarean section (71). In the adult animal the reduction of a circulating bed even of the same resistance as the total vascular bed, raises the arterial blood pressure (23). In the human, contraction of the uterus during labor probably reduces both the maternal and fetal placental blood flow and therefore much of the low resistance circuit of the placenta is gradually removed before the arterial pressure measurements are made as the cord is tied. Other hemodynamic factors, such as the relative distribution of blood between the fetus and the placenta and the relative proportions of the cardiac output which traverse the placenta, might also influence any change in systemic pressure at birth. In the lamb, at term, only 15 per cent of the total blood volume is to be found in the placenta and 60 per cent of the cardiac output traverses this vascular bed. The human placenta contains 30 per cent of the total circulating blood volume at term (173), but the portion of the cardiac output perfusing it is not known.

Ashworth & Neligan (14) have used the conventional inflatable cuff and manometer and a sensitive pulse indicator to measure the arterial pressure in the newborn infant's arm, and report marked changes in systolic pressure within the first 24 hours of life. The initial pressures, within 2 min of delivery, ranged from 116 to 52 mm Hg and there was subsequently a fall of up to 54 mm Hg (fig. 21); delay in clamping the cord postponed this fall, but

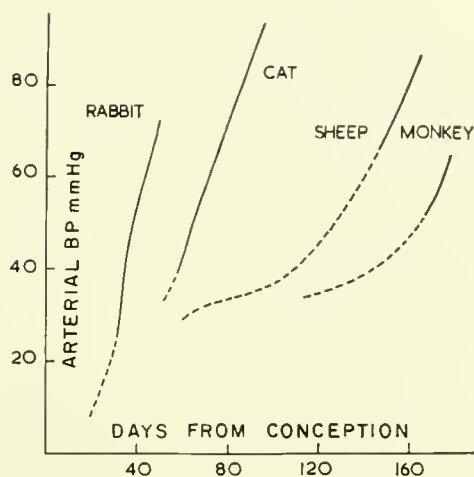


FIG. 22. Arterial blood pressures before (----) and after (—) birth, showing the continuous course of the rise with increasing age, in the rabbit, cat, sheep, and monkey. (Modified from G. S. Dawes. Changes in the circulation at birth. *Brit. Med. Bull.* 17: 150, 1961.)

did not influence its magnitude. It is tempting to suggest that the wide range of initial pressures is due to varying degrees of asphyxia during birth, but no proof exists for this explanation. The pressures rise gradually during the second day of life and during the subsequent weeks.

Once the temporary interruptions of parturition are over, the mechanisms which have been responsible for the gradual rise in arterial pressure throughout gestation will, probably, be extended into the neonatal period: these mechanisms are, however, likely to be modified by the different internal environment of the young free animal, as compared with the fetus, and by many other factors which will vary with the species; orthostatic factors and the mode of life will be among these. The rate of rise in arterial pressure is rapid in small animals and the mean pressure is about doubled during the first 6 weeks of life, approaching the adult level; in the sheep and monkey the rise is slower (fig. 22). In the human infant, who has been a repeated subject for blood pressure measurements, the rise is slow during the first 9 months of life (fig. 23) and continues well into adolescence and throughout adult life (194). [But see also (193). Ed.]

The newborn is a more satisfactory experimental subject than the fetus for, under experimental conditions, an established respiration provides a more constant internal environment than the placental circulation. The differences between the cardiovascular responses of newborn and adult animals are of a quantitative rather than a qualitative nature:

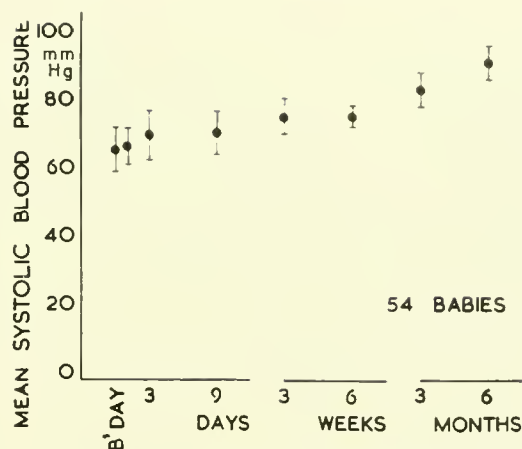


FIG. 23. Mean arterial blood pressures at birth and during the first few months of life in normal infants. [From Holland & Young, *Brit. Med. J.* 2: 1331, 1956.]

in the newborn monkey there is evidence for functional baroreceptor and chemoreceptor activity, yet bradycardia and hypotension still follow acute hypoxia (71). In the young growing rabbit (70, 83), kitten, and puppy (114) a gradual increase in vasoconstrictor tone in the systemic circulation can be demonstrated by the responses to asphyxia and to the injection of hexamethonium. Downing's (83) observations show that the threshold for baroreceptor stimulation in young rabbits is about 40 mm Hg. Hutchinson *et al.* (114) have also demonstrated in the newborn kitten and puppy that the carotid sinus-cardiac center mechanism will respond to a rise in pressure but not to a fall. These findings may be explained by Landgren's (126) observations that 40 mm Hg is just within the recording range of the baroreceptors; any stimulus which raises the pressure will elicit a response, especially if the pulse pressure is also increased (85), but a further fall will be ineffective. As the resting arterial pressure rises and approaches the maximum sensitivity range of the baroreceptors, 85 to 100 mm Hg, the reflexes become more active; for instance, following the injection of adrenaline the percentage decrease in heart rate increases in relation to the percentage rise in blood pressure in the growing rabbit and kitten. The direct action of adrenaline on the heart could only be demonstrated in the youngest animals following doses so small that the blood pressure did not rise sufficiently to elicit a reflex bradycardia. In contrast, the young kitten heart was found to be more sensitive to acetylcholine than the peripheral vessels; with small doses a marked bradycardia accompanied the fall in blood pressure in the kitten, while reflex

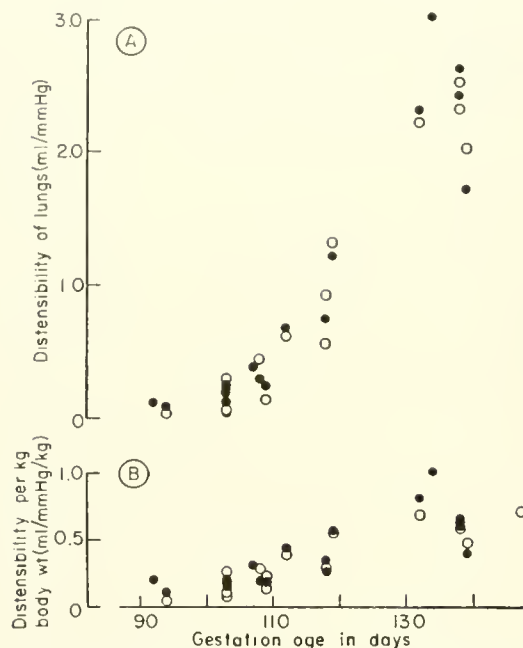


FIG. 24. Increase in distensibility of fetal lamb lungs with age. *A*: tidal air/peak intratracheal pressure = distensibility; *B*: distensibility per kg body weight plotted against age. [From Dawes (66).]

tachycardia followed the hypotension occurring with comparable doses in the adult.

In the newborn monkey, the carotid sinus reflexes are functional and occlusion of the carotid arteries has been shown to cause a rise in the arterial pressure, which is abolished by cutting the carotid sinus nerves (71); but acute anoxia causes a fall in arterial pressure suggesting that the vasomotor center itself is not very active: there was, however, a rise in arterial pressure in the fetus in response to asphyxia. In the newborn baby the mean arterial pressure is about 40 mm Hg below the mean pressure of the adult and the available evidence shows that, once the immediate readjustment of birth are complete, there is a low peripheral resistance (196); the cardiac output per kg of body weight is about double that of the adult, the blood flow to the extremities is likewise double and the cerebral blood flow is high (123). Low tonic activity of both the chemical and reflex regulating mechanisms are probably concerned, and the development of these will probably contribute relatively more to the gradual rise in arterial pressure during growth than the cardiac output, which declines in relation to body weight. Recently, records of arterial blood pressure changes during replacement transfusions, when the blood volume was reduced rapidly by 10 per cent, demonstrated that the baroreceptor

mechanisms are not very active in the newborn infant (197). The physiological activity of the vasomotor sympathetic mechanism to the skin blood vessels is, however, well developed at birth and quite comparable with that of the adult—a fact which was demonstrated clearly by Day (79) who showed, by conductivity measurements, that the circulatory responses to changes in environmental temperature were as effective as in the adult in maintaining body temperature. These observations have recently been amplified by Brück (47).

Renal blood flow appears to be low in the sheep fetus (5) and the newborn infant (173) when compared with the adult on a body weight basis; PAH clearance was used in these measurements but nothing is known of the secretory capacity of the tubules for this substance. Unilateral renal artery stenosis, with fatal arterial hypertension of 180 mm Hg, has been observed in a newborn infant (130) suggesting that the renin-hypertensinogen mechanism is active early in life in man and may account for the hypertension above the lesion with coarctation of the aorta.

Viability

Viability, in its narrowest sense, may be considered as the capacity of the newborn to establish correct

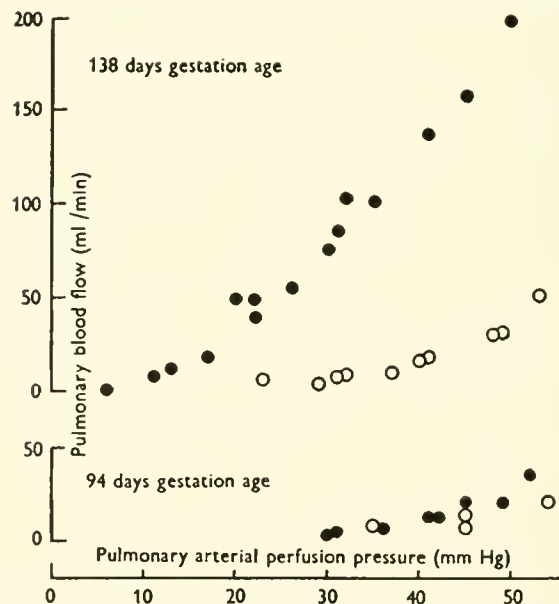


FIG. 25. Perfusion of isolated lungs of two fetal lambs, mature, above; nonviable, below. Pressure flow diagrams were constructed before ventilation (○) and about 15 min later (●). Following ventilation, there is a large decrease of pulmonary vascular resistance in the mature lamb and almost no change in the premature. [From Dawes (66).]

pulmonary ventilation and perfusion to provide full oxygenation of the blood in order to maintain the necessary oxygen supply to the body tissues; it is, therefore, closely linked with lung development which occurs relatively late in intrauterine life. Most of the quantitative data relating this development to length of gestation are, again, supplied by Dawes and his colleagues in the lamb fetus. At 90 days of age fluid starts to collect in the alveolar spaces of the lungs (93). Shortly afterward the distensibility of the lungs begins to increase so that, at a given inflation pressure, older lambs obtain more tidal air per kg body weight (fig. 24); ventilation also starts to cause a decrease in pulmonary vascular resistance and there is a larger blood flow for the same perfusion pressure (fig. 25). By 110 days gestational age, about 28 to 30 weeks on the human scale, artificial ventilation can raise the arterial oxygen saturation to 95 per cent and independent existence is possible; in the nonviable premature this cannot occur and death is due to asphyxia.

The development of many other physiological mechanisms must also influence the successful operation of ventilation and perfusion of the lung tissues. Among these will be the level of the arterial blood pressure, closure of the foramen ovale and ductus arteriosus, and the presence of sufficient surface active substance to prevent collapse of the expanded alveoli (145); Avery & Mead (18) have found the surface activity of lung extracts from premature infants to be only one-third of that from normal full-time lungs.

Congenital Heart Disease

The transition from the fetal to the adult course of the circulation may not take place because of in-

herent congenital abnormality or be protracted on account of a difficult labor and the ensuing asphyxia. Rowe (164) gives a concise account of the physical signs and the physiology of both, together with the possibilities of their treatment (122). The physiological disturbances accompanying congenital malformations may be divided into three groups: 1) a left-to-right shunt through a patent ductus arteriosus, 2) the retention of a fetal type of flow through both ductus arteriosus and foramen ovale, and 3) simple intracardiac arteriovenous shunts. Only the first group have normal arterial oxygen saturations.

The physical signs of congenital heart disease are frequently difficult to distinguish from the transient abnormalities due to respiratory disturbances at birth; Rowe also divides these infants into three main groups. In the first are those who do not breathe readily at birth and who have a murmur due to patency of the ductus arteriosus: Burnard (51) has observed a midsystolic murmur in 70 per cent of such infants, and considers it due to swift turbulent flow through a ductus only partially constricted on account of asphyxia; the direction of this flow will depend upon the relative pressures in the pulmonary and aortic trunks. Lind & Wegelius (129) have angiocardigraphic evidence for delayed closure of the ductus arteriosus following asphyxia neonatorum. In the second group, apnea may develop suddenly following normal respiration of a few hours to 4 weeks duration; a loud continuous murmur, due to a left-to-right shunt through the opened ductus arteriosus is heard. The third group of premature infants, with classical respiratory distress syndrome have, on account of the high lung resistance, a pulmonary ejection click to the second heart sound; during the recovery phase a midsystolic sound is also heard as the ductus arteriosus narrows.

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The flow of blood through bones and joints

WALTER S. ROOT *Department of Physiology, College of Physicians and Surgeons, New York City*

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BONE MUST NOT BE thought of as an inert substance, but rather as one of the highly specialized tissues of the body, consisting of active cells which respond promptly to physiological demands upon the skeletal and hematopoietic systems. The cells are sensitive to nutritional and functional processes, and differ in their reactions from those of other tissues only because of the rigidity and stability of the intercellular deposits of mineral salts.

Contrary to general belief, bone is a relatively vascular tissue (68). This concept is borne out by the rapidity with which substances injected into bone marrow appear in the general circulation (105, 106). Large infusions can be administered in a short time (4), and this route of giving fluid has been useful in dealing with infants (43) and in treating patients in conditions of hemorrhage and shock (101).

BONES

The anatomical features of the vascular system in bones are classified as long bones, flat bones, or vertebrae.

Long Bones

Most studies of the long bones have been made upon the femur or the tibia-fibula. The long bones receive blood from three sources: *a*) the nutrient artery or arteries entering the bone in the shaft, *b*) blood vessels entering the ends of the bone, and *c*) blood vessels penetrating the periosteum (fig. 1).

Radiological observations in which the arteries are injected with radiopaque substances show that the principal nutrient artery of the femur traverses the cortex inclined toward the knee (16). No branches are given to the cortex in the nutrient canal. On entering the medulla, the artery divides into ascending and descending limbs which, with few subdivisions, pass to either end of the bone. In general, larger arteries are visualized as sharply defined and tortuous channels in the proximo-distal axis, and are comparatively few in number.

Medullary arteries can be traced to the metaphyseal region where they break up into numerous fine vessels which join across the line of union at the epiphyseo-metaphyseal synostosis with others derived from the epiphyseal arteries (fig. 2). Arterial twigs from the main medullary arteries can be seen to pass more or less transversely toward the endosteal aspect of the compactum where they recurve and course for a short distance in the peripheral medullary zone. Here they anastomose with one another, and give rise to fine vessels which pierce the endosteal face of the compactum and arborize irregularly in the inner cortical zone (16).

There has been some difference of opinion concerning the vascular supply to the metaphyseal region. Thus, Weinmann & Sicher (111) state that the nutrient artery supplies the central part of the metaphysis, its more peripheral parts being fed by metaphyseal arteries derived from the periosteum. On the

other hand, Trueta & Harrison (107) believe that in the adult human femur the nutrient artery does not reach the metaphyseal region which is wholly supplied by metaphyseal arteries. Studies on rabbit embryos and young rabbits indicate that in the earliest stages of development the metaphysis receives blood only from the nutrient artery. Later, metaphyseal arteries derived from the periosteum take over the supply of the peripheral region, the extent of the area supplied by them increasing progressively (85).

The arteries supplying the proximal part of the femur and the acetabulum are the lateral femoral circumflex, the medial femoral circumflex, the obturator, the superior gluteal, the inferior gluteal, the first perforating artery, and the nutrient artery of the femur (62). Branches of these enter the head and neck of the femur through small foramina, or enter by way of the fovea centralis, or are carried to the head of the femur in the ligamentum teres.

In children the foveal vessels assume a small role in supplying blood to the femoral head (108, 114). When these arteries do penetrate to the ossification center they are probably supplementary (62). In the adult the foveal arteries are larger and usually nourish the femur. Apparently, arteries enter the femoral head through the ligamentum teres in the majority of cases (108, 114), but this supply is supplementary to the vital supply from the capital arteries (62).

All investigators have emphasized the importance of the capital branches of the medial femoral circumflex artery for the nutrition of the femoral head (109). The terminal branches enter the femoral head at the articular rim, just posterior to the superior and inferior poles of the femoral neck. Most investigators have found that the superior posterior branches are larger and more numerous than the inferior posterior arteries. Usually, no arteries enter the femoral head or neck anteriorly (109). The nutrient artery cannot be traced past the marrow cavity (62).

Vessels enter the distal end of the femur through three groups of foramina: supracondylar, condylar, and intercondylar (99). In each some 10 to 35 for-

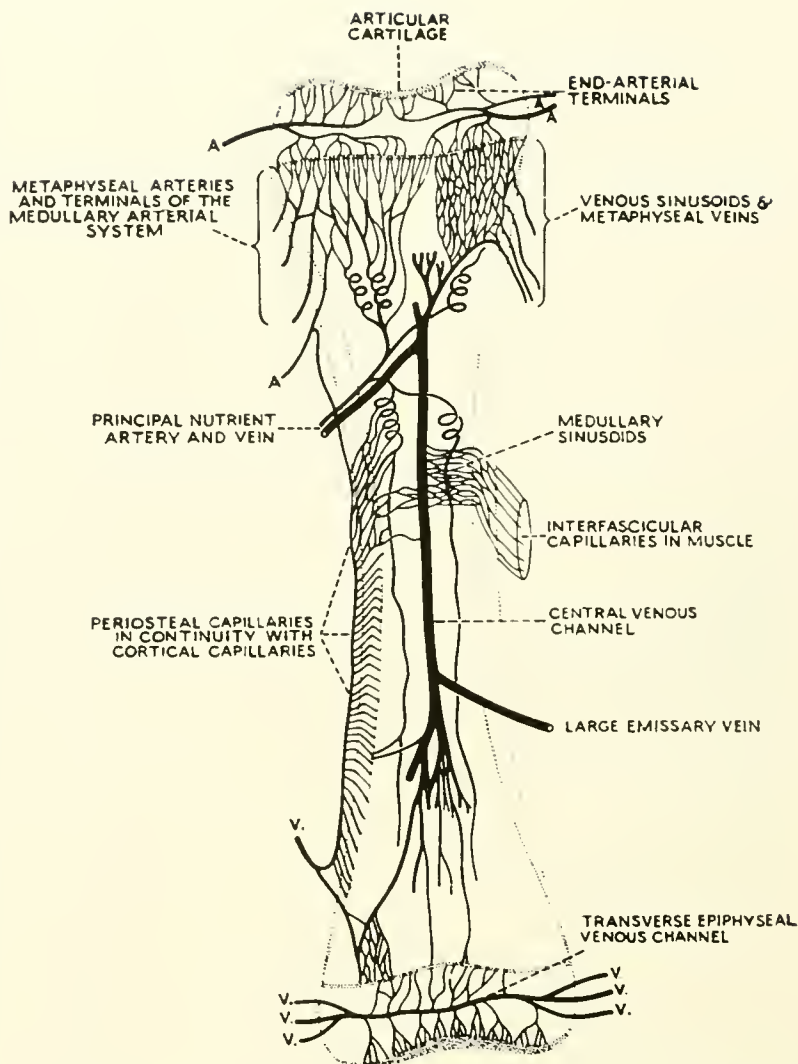


FIG. 1. Diagram of vascular organization of rat tubular bone in longitudinal section. [From Brookes (13).]

amina are present. Condylar arteries perforate the cortex and ramify within the spongiosa. Terminal branches of the middle geniculate arteries pass through the intercondylar foramina and are distributed to the central parts of the epiphysis. Rami arising from the superior, lateral, and middle geniculate arteries pass through the anterior and posterior supracondylar nutrient foramina, and are distributed to the distal end of the diaphysis. The generous vascular supply explains the lack of ischemic necrosis after fractures of the lower end of the femur.

The blood supply to the cortex or compactum of long bones runs in longitudinal canals known as Haversian canals. In man the canals vary from 25 to 125, averaging $50\ \mu$ in diameter, but larger ones are also seen (70). Although these canals run longitudi-

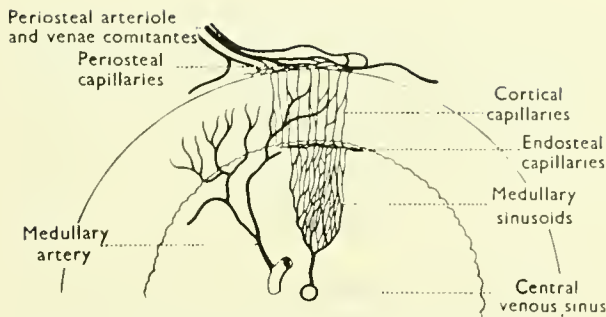


FIG. 2. The blood vascular organization of diaphyseal tubular bone represented diagrammatically in transverse section. [From Brookes (14).]

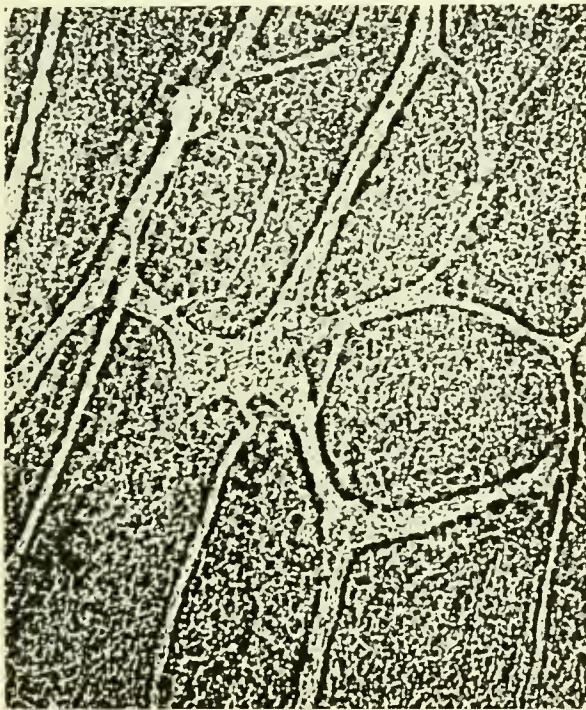


FIG. 3. A longitudinal section of cortical bone showing the anastomosing and branching Haversian canals. The communicating canals between the Haversian canals are demonstrated. [From Jaffé (70).]

nally, they do not run vertically for more than short distances soon deviating from a straight line. The canals form a continuously anastomosing and ramifying network (fig. 3). Beneath the articular cartilage at the upper and lower ends of a bone, the canals run transversely to the long diameter of the bone. Near the surface of the bone, Haversian canals communicate with the canals of the ground lamellae which open to the external surface of the bone, and the innermost canals lead into the medullary cavity. Re-

cently the term "macrocanicular system" has been used to refer to the system in mineralized tissue which is made up of Haversian and anastomosing Volkmann spaces (68). It is generally stated that one or two capillaries are present in an Haversian canal (79). A single endothelial tube surrounded by a slight adventitia has been described in Volkmann's canals.

Lexer (86) had emphasized the role of the periosteal arteries in bone nutrition, but more recent studies indicate that the periosteal circulation may be scanty (20), periosteal arteries being found rarely or only with difficulty (1). Also, the notion of a periosteal arterial penetration of compact bone has recently been rejected as a result of microradiographic analysis in the rabbit (16), and in the rat and human fetus (13, 14). This opinion is further strengthened by a study of nonischemic adult tubular bone (15). According to certain investigators (13-16), normal diaphyseal blood flow is centrifugal, that is, passing from the medullary arterial system outward through the cortex into the periosteal and interfascicular capillaries of muscle. Drainage of compact bone is effected either by way of periosteal capillaries or through medullary sinusoids and the central venous channel. Apparently, the vascular systems of bone and periosteum are united, but only at the capillary level. This would explain the survival of outlying bone cells seen by Marneffe (88) in rat diaphysis nourished by the periosteum alone. It also provides a basis for the development of a collateral circulation as found in Johnson's experiments in dogs (72).

The obliquity of Haversian canals has been noted by Cohn & Harris (29) and others. Brookes (13), studying rat femora and tibiae as a whole, was able to show how cortical vascular obliquity is in opposing senses at either end of a long bone, the two regions meeting by abrupt directional changes. In the adult human tibia this change takes place at the inferior metaphysis and may well be a factor in the delayed healing of fractures at this site, where a rich venous outflow would predispose to recurrent hematoma formation.

It seems likely that the normal arterial supply to cortical capillaries is mediated by medullary end arteries. This conception is supported by the findings of Eletto (42) who noted the lack of anastomoses between branches of the principal nutrient artery in the medulla. It would help to explain the occurrence of irregular bone cell necrosis in the cortex produced by the injection of particulate suspensions (75, 76), or by interruption of the principal nutrient artery (10). Epiphyses also seem to contain discrete circumscribed

vascular zones with little functional overlap, the obstruction of which on either arterial or venous sides is a factor in osteochondritis juvenilis (19).

The role of the periosteum in bone regeneration and the incorporation of blood vessels from the periosteal vascular network during bone growth in width can still be accepted in that the vitality of the osteogenic layer of young periosteum is maintained by the osteogenic capillary layer fed by periosteal arteries (54).

As visualized radiographically, the venous system differs somewhat from the arterial system. Thus, a solitary longitudinal channel of wide caliber in an approximately central medullary position can be traced from one end of a bone to the other. Since this central canal lacks a muscular tunica media (88), it may properly be called a central venous sinus in the medulla (16). At the trochanteric fossa the central venous channel is joined by tributaries from the lesser, third, and greater trochanter as well as by a vessel passing down the neck from the head of the femur. The central vein is joined by the principal nutrient vein a short distance below the nutrient canal and passes characteristically as a single vessel down to the inferior metaphysis where it anastomoses with an ascending branch of the middle geniculate vein. Sometimes it divides into two stems at the mid-shaft level. The central venous channel has numerous transverse branches radiating toward the endosteum and these drain the sinusoids of the medulla. An endosteal line marking the junction of the medullary sinusoids with the cortical capillaries can be seen.

Branemark (11), who has been able to visualize bone circulation in the living rabbit, states that the bone marrow arteriole divides dichotomously into capillaries. These run to sinusoids which are sometimes hexagonal, sometimes spindle shaped. Sinusoids may unite to form sinusoidal systems. The sinusoids are drained by venules into collecting venules which empty into the central veins. The sinusoids vary rhythmically in their degree of dilation. Blood cells may bypass a sinusoid by flowing through a shunting capillary directly into a venule. In some instances, cells appear to hug the vessel wall of one half of a sinusoid apparently without disturbing flow in the other half. Capillaries stemming from marrow arterioles enter the Haversian canals to supply endosteal parts of diaphyseal bone. The capillaries then swing back into the marrow to empty into sinusoids or directly into collecting venules. Blood flow in bone capillaries is fairly steady, and the velocity of flow is higher than in marrow capillaries.

In the pigeon, "transitional capillaries" (37, 38) connect the arteries to the venous sinusoids. The capillary link is extremely circumscribed, and it is not until the venous sinusoidal anastomoses are reached that the blood spreads out in lacing and interlacing vessel tufts, thence to be directed from the tuft-like branchings into larger and larger vessels eventually to enter the central longitudinal vein almost at right angles.

There seems little doubt that the extensively distributed, spacious, thin-walled venous sinusoids normally form the principal functioning vascular bed for the actively circulating blood in marrow, i.e., they correspond to the capillaries of other organs.

In pigeons in which the marrow is made hypoplastic by starvation, one can see, between the fat spaces, well-outlined and clearly defined channels which constitute a most extensive system of capillaries (37). Many of these appear to be nonpatent and functionally dormant as far as the active blood circulation is concerned. These capillaries come off the venous sinusoids by way of conical openings, and seem to be continuous with them. They are not capillaries in the sense of an arteriovenous transition, but instead extend from venous channel to venous channel; they are intersinusoidal. The same intersinusoidal semi-collapsed channels have been reported in the marrow of the ribs of the white rat (38), and are believed to be present in the dog (40).

Three theories as to the nature of the circulation in adult marrow have been advanced: *a*) by Rindfleisch (98) who believed that the blood spaces are lined by parenchyma alone and have no endothelial cells; *b*) Langer (81), on the other hand, thought of the mar-

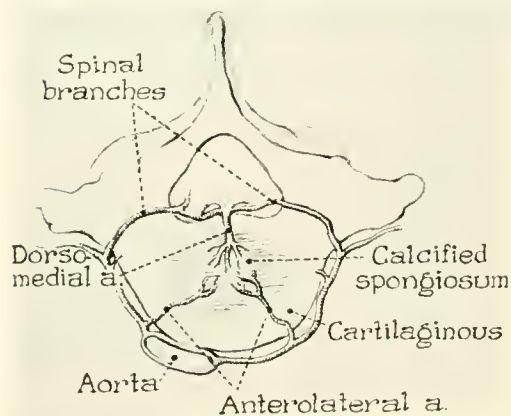


FIG. 4. Diagram of a transverse section through the mid-body of the vertebra of a six-month-old fetus. [From Ferguson (46).]

row as an entirely closed vascular system; and *c*) Bunting (18) pictured vessels lined with epithelium, but with openings at various points communicating directly with the medullary parenchyma. A survey of the literature indicates no general agreement among those who have studied the subject.

Vertebrae

In the lumbar and thoracic regions the aorta gives off paired segmental arteries. These penetrate the anterior groups of spinal muscles and continue posteriorly in the horizontal plane to pass on either side of the vertebral body and lie in direct contact with the anterior and lateral wall of this structure (fig. 4) to which small branches are contributed (56). Each artery gives off a large branch in the trough formed by the vertebral body and the transverse process. This branch traverses the intervertebral foramen and divides into three terminal arterioles (113). One of these passes to the posterior surfaces of the two adjacent vertebral bodies. A second runs to the spinal cord and its meninges. The third supplies the posterior vertebral processes and surrounding soft structures.

The first branch mentioned above divides within the spinal canal, one terminus running upward and medially across the posterior surface of the vertebral body under the posterior spinal ligament, to enter a foramen about the center of the body. The other terminus runs downward and medially to a similar entrance in the center of the body of the next distal vertebra. Thus, there are four diagonal arteries, two from each side converging to enter the center of the posterior surface of each vertebra, either through a common foramen or through separate foramina. The arterioles may coalesce or remain separate before radiating to all parts of the centrum (113). The main dorsal vertebral artery and the right and left anterolateral arteries appear to end in the middle of the developing osseous spongiosa. No arterial branches can be demonstrated beyond the center of the vertebral body. Irregular vascular canals can be seen in the spongiosa and a diffuse network of thin-walled channels is present in the surrounding cartilaginous zone. Very small vessels perforate the cartilaginous plate and tiny capillary channels permeate the canulus fibrosa. The branches to the cord anastomose freely with the anterior and posterior spinal arteries which lie on the respective surfaces of the cord extending from within the skull to the end of the cord. The pedicles, transverse processes, articular facets,

and lamina have a good arterial blood supply through the anastomosing branches of the posterior rami from the paired segmental arteries (46). Similar anatomical arrangements are true for the cervical vertebrae (56).

The intervertebral disc tissues appear to offer an important focus for degeneration as they are always farthest from the arterial supply (46).

Each lumbar vertebral body is drained by four main venous trunks. Two leave the body, one on either side from an anterolateral position at a level just above the midline; two emerge as paired vessels from the bony foramen in the center of the posterior vertebral wall (110). The two posterior veins empty at once into the anterior longitudinal meningo-rhachidian veins of the posterior external plexus. Direct connection with the corresponding lumbar veins is made through the spinal rami of the latter. The two anterolateral veins from the vertebral body empty directly into the lumbar veins. The lumbar veins passing horizontally are in direct communication with three great longitudinal or vertical venous systems: *a*) posteriorly with the posterior external venous plexus which extends vertically within the spinal canal, external to the spinal cord membranes; *b*) with the azygos or hemiazygos systems, and *c*) with the inferior vena cava.

Within the vertebral body the two posterior and the two anterolateral veins meet to form a large reservoir. Although these veins have the usual venous structure beyond the vertebral periosteum, the wall structure is replaced by a limiting membrane of flattened endothelial cells within the body. Radiating peripherally from the central venous basin are many irregular columnar spaces which occupy approximately forty per cent of the entire vertebral body. The more peripheral parts of the venous spaces contain within their lumens a very large proportion of hematopoietic tissue, together with reticuloendothelial elements. Hematopoietic tissue is occasionally found within the lumen of the central venous space (110).

Flat Bones

The mandible appears to be the flat bone concerning which the most information is available. The periosteum and outer circumferential portions of the osseous mandible are supplied by such adjacent arteries as the facial, submental, inferior alveolar, mylohyoid, mental, masseric, lateral pterygoid, medial pterygoid, temporal and sublingual branch of the lingual (36). One or more nutrient foramina passing

through the marrow space are evident above the genial tubercle, and multiple small foramina are usually seen in the small triangular area on the inner face of the ramus below the mandibular notch and above or on the endocondylar and endocoronoid ridges.

Within the mandibular canal the inferior dental artery gives rise to blood vessels which pass upward toward the alveolar border (28). Some vessels pass toward the lower border, but these are few in number. The lower border of the mandible is supplied mainly by periosteal vessels. The inferior dental artery within the mandibular canal is surrounded by numerous vessels, presumably *venae comitantes*.

Some eleven areas of cortical bone are recognized (36), the regions being based upon the direction of the canals in the Haversian mesh. There is little evidence of the presence of lacunae or canaliculi in the adult.

Nerve Supply of Bone

Perhaps the most complete and careful study of the innervation of bone has been carried out by Kuntz & Richins (78). According to their study the absence of any nerve fibers not in close proximity to blood vessels, in preparations in which excision of the dorsal root ganglia had resulted in degeneration of the afferent fibers, leads to the conclusions: *a*) that the parenchymatous tissue of the bone marrow is devoid of direct afferent innervation, and *b*) that, in preparations of normally innervated bone marrow, unmyelinated fibers which exhibit no obvious relationships to blood vessels represent unmyelinated afferent fibers or the unmyelinated terminal portions of myelinated ones.

AFFERENT FIBERS. The conception of some sensory innervation of the bone marrow is supported by the common clinical observation that puncture of bone gives rise to pain, and the finding that many afferent fibers in bone fall within the caliber range of the pain-conducting fibers is in full agreement with this view. Schleicher (100) noted that when blood plasma was infused into the sternum a sharp pain was felt about the infusion area when the pressure of the incoming fluid was greater than the intramedullary pressure. In many persons with multiple myeloma and metastatic bone lesions, distinct bone pain is associated with sudden straining or coughing (94). It is possible that the sudden elevation of intramedullary pressure shown to result from such effort results in

distortion of the arteries and arterioles bearing sensory nerves and that this produces pain.

When the sympathetic nerve fibers are caused to degenerate by removing the appropriate sympathetic ganglia, afferent fibers are found running to blood vessels. They are present in relationships which indicate that they are also connected with receptors imbedded in the parenchyma of the marrow (78). Foa (47, 48) suggests that the afferent fibers may play a part in the reflex regulation of functional activity of bone marrow, and Chiray *et al.* (24) have shown that the intramedullary injection of certain substances will produce reflex changes in blood pressure.

EFFERENT FIBERS. The relation of the sympathetic innervation to bone circulation has been studied either by sectioning or stimulating sympathetic fibers. It seems clear that cutting sympathetic fibers causes vasodilation and hyperemia (39, 40, 48, 60), and that stimulation produces vasoconstriction (39, 48, 60, 112).

Hurrell (69) has traced nerve fibers into and along Haversian canals of adult bone into two-thirds of the thickness of the shaft of a cat's femur. Some end blindly in the bone matrix; others, in close connection with osteocytes. He suggests tentatively that the nerve fibers found may be the two ends of a reflex arc governing bone growth and maintenance. In this connection Coppo (31) has reported a decrease in the percentage of ash, and a modification of its composition, 8 to 15 days after denervation of bone. Nevertheless, all experiments on animals have shown that unilateral sympathectomy by itself has no observable effect on bone growth (3, 21). The results obtained from experiments on the effect of sympathectomy on the healing of fractures are equivocal. Some investigators have found healing to be accelerated (30), whereas others have seen no effect (89). According to Corbin & Hinsey (32), bones and joints are not supplied with nerves having specific trophic functions.

Blood Flow in Bone

The circulation in bone is sufficient to supply the normal variations of physiological processes, but often fails to respond to the extreme insults of trauma or infection. The delayed union of comminuted bumper fracture of the tibia, and the extensive involvement of the shaft of the long bones in osteomyelitis are classical examples. In situations where end arteries are present, as at the metaphyseal side of the epiphyseal plate, infarction is common. Aseptic infarction is

found in nutritional diseases such as scurvy and rickets, and septic infarction with abscess formation in tuberculosis and other forms of bacteremia (23).

Arterial blood from the terminal arborizations in the cortex, derived from the medullary arterial system, empties into a vascular lattice contained in the canals of Havers and Volkmann (16). Here the circulation is probably very sluggish and, besides movement up and down the diaphysis, blood may be shifted into either medulla or periosteum depending upon functional variations in opposing muscles and hematopoietic activity in the marrow. According to Branemark (11) blood flow in bone capillaries is fairly steady and the velocity is greater than in marrow capillaries. Externally, the vascular lattice of the cortex connects with the osteogenic capillary layer; internally, with the medullary sinusoids. The former route to the systemic veins is direct and probably drains most of the blood circulating in the cortex. The latter route is indirect, through the sinusoids, into the central venous sinus, and thence via the nutrient vein at the bone extremities into periarticular veins (16).

Lamas *et al.* (80) have pointed out that a relatively slow blood flow in bone should be expected, since none of the three functions of long bones, mechanical support of the body, storage of calcium salts, and hematopoiesis, needs a rapid circulation. In this connection, it may be noted that the arrangement of blood vessels within bone favors a slow circulation. Thus, the nutrient artery describes many curves before entering bone and after dividing into ascending branches which run through the marrow, it ends in wide blood spaces close to the epiphyses. These blood spaces are in close contact with thin-walled veins of wide caliber. This arrangement of blood vessels reduces the pressure and speed of circulation in the arteries, and enables the vein to carry substances quickly away from the blood spaces; hence the efficacy of therapeutic injections into marrow.

Few quantitative studies of blood flow through bone have been made. Jones (73), who studied the uptake rate of a radioactive colloid which is highly selected by marrow cells, found a minimal circulation through the red marrow in the rabbit amounting to 7 per cent of the circulating blood volume per min. A corresponding value for man would be about 300 ml.

The blood flow through human bone has been studied by measuring the rate of clearance of I^{131} from bone marrow (94). No apparent correlation was found between marrow clearance rates and hemoglobin level, leucocyte count, body temperature, or

blood pressure. The intravenous injection of hexamethonium bromide, a ganglionic blocking agent, reduced the clearance rate of marrow, and this appears to be directly related to the fall in blood pressure. Conversely, the injection of Paredrine resulted in a distinct increase in the clearance rate from the marrow, presumably as a result of the sympathomimetic action of the drug. A decreased flow through the perfused tibia of the dog can be produced by stimulating sympathetic nerve fibers or by adding Adrenalin to the perfusion fluid (39).

Plethysmographic measurements of blood flow through the normal humerus of man have been made by Edholm *et al.* (41). They report a blood flow through the nutrient artery of 0.5 to 1.0 ml per 100 ml of bone per min. They point out that this value may represent only half the total flow, for the periosteal vascular supply is not included. They calculate on the basis of these measurements that the total skeletal blood flow should be 74.5 ml per min, although they concede that this is bound to be an underestimation, for bones with an active marrow are more vascular than the humerus. The above measurements are much lower than the values of 3.5 to 41 ml per 100 g bone per min found in perfusion experiments using the tibia of the dog (40).

HYPEREMIA. Blair (7) has suggested that alternating ischemia and hyperemia maintain normal bone calcification and aid healing after a fracture. In this connection it should be noted that hyperemia has long been thought to be the physiological basis for localized deossification. Thus, Leriche & Policard (83) state: "If by any process whatever, the activity of the circulation is increased in the vicinity of bone, the latter becomes rarefied." Also, Greig (52) has written: "Every trauma of bone is followed by a reactionary local hyperemia, and every disease resulting in bone rarefaction or decalcification is accompanied by a more or less copious and prolonged increase of the arterial and capillary circulations." De Lorimer *et al.* (87) interpret their radiological studies showing areas of bone rarefaction as being the result of localized reflex hyperemia. They believe this may be produced by trauma even of minor degree as in simple contusions, sprains, or overenergetic physical therapy, or by infection or neoplasms.

Although the above statements seem to rest more on logic than on observable facts, it seems clear that vascular resorption of bone is related to definite circulatory changes. Thus, Miller & de Takats (91), who carried out plethysmographic studies of blood flow on

12 patients suffering from painful osteoporosis following injury, found an increased blood flow amounting to 5 to 60 per cent in the affected limb. Also, in severe inflammatory processes an actual coalescence of several Haversian canals takes place, the bony partition between them disappearing with the formation of large spaces in bone containing numerous blood vessels and considerable vascular granulation. The process is not confined to the Haversian system, but also involves the spongy tabeculae. The marrow also becomes extremely vascularized, as a result of the proliferation of the existing vessels (71).

REDUCTION OF BLOOD SUPPLY. According to Haslhofer (58) the richness of anastomoses in long bones prevents bone infarction even when the blood supply to the nutrient artery is interrupted. On the other hand, Axhausen & Bergmann (2) present clinical instances of aseptic bone necrosis which they ascribe to interruption of local blood supply. Also, Phemister (96, 97) has published radiographic and pathologic descriptions of lesions which he considers to be the result of marrow infarction.

Since the production of bone and marrow infarcts in animals was generally considered impossible by conventional means, earlier investigators resorted to extensive stripping procedures or to the production of multiple small emboli designed to occlude large numbers of capillaries. Thus, Brunschwig (17) attempted to produce infarction of the marrow of the femur in dogs by stripping the entire periosteum and simultaneously cutting the nutrient artery. Despite this extensive trauma, no evidence of infarction was seen in adult dogs. Among the injection experiments are those of Wollenberg (115) who injected talc into the femoral artery of dogs and observed areas of necrosis in metaphyses and epiphyses. Bergmann (6), on the other hand, could find no changes in epiphyses, although he saw widespread necrosis of cortical bone after the injection of particles of silver suspended in gum arabic, and Kistler (75-77) could find no infarcts following ligation of the nutrient artery of the femur in rabbits. However, the injection of suspensions of charcoal in acacia and of masses of agglutinated bacteria, under unmeasured but admittedly high pressure, produced areas of necrosis in the center of the metaphyses.

Huggins & Wieve (65) seem to have been the first to report changes following occlusion of the nutrient artery only. In both mature and immature rabbits ligation of the nutrient vessels to the femur was followed in all instances by infarction of the marrow.

Although in a few cases there was some periosteal and endosteal reaction above the operative site, no evidence of bone infarction was found. In a recent study Brookes (12) has shown that occlusion of the principal nutrient canal of the femur in day-old rabbits produces an initial shortening, followed by equalization, and then a final absolute shortening of 3 per cent in the occluded femur.

Variations in nutrition of the growth cartilage will cause shortening or lengthening of long bones. Thus, interruption of the medullary arteries and diversion of blood to the growth cartilage presumably will account for the increased growth rate observed in long bones affected by a variety of conditions, such as fractures, chronic infections, and tumors (45). Occlusion of the nutrient canal may result in diversion of blood into the epiphyseal and metaphyseal arteries, with possible ischemia of the diaphysis. It is probable that while collateral circulation is developing in the bone extremities, a diminution in the femoral blood supply to the growth cartilages occurs, thus accounting for the growth lag of occluded femora noted by Brookes (12) in the first 30 days. With the establishment of a collateral circulation by means of anastomoses between the metaphyseal arteries and the principal nutrient artery, blood flow near the growth cartilage is increased bringing about equalization in the length of occluded and normal femora in the intermediate growth phase. In the final phase, 120 to 150 days, a relative decrease in the nutrition of the growth cartilages must occur to account for the 3.7 per cent retardation in femoral growth seen at maturity. The reason for this is not clear. However, it seems probable that towards the end of growth the collateral circulation is not quite able to furnish the same quantity of blood to the medullary artery as when the nutrient artery is also available as a supply channel (12). These results may be compared with the evidence of bone lengthening after fractures in children (22) in whom presumably the same local vascular mechanism is active that determined the growth curve of occluded femora in rabbits.

It is generally thought that the disturbances on the venous side produced by obliterating the vein accompanying the nutrient artery is slight, because of the profuse venous drainage at the bone extremities (57) and at the surface of the diaphysis (16).

Oxygen in the Blood of Bones

Ham (53) has shown by measurements in the dog's radius that bone cells, if they are to survive, can gen-

erally be no farther than $100\ \mu$ from a nutrient vessel. Actually few quantitative measurements of the oxygen content of the blood circulating through bone have been made, and these have been concerned with the blood taken from marrow. Thus, Grant & Root (51) punctured the humerus of unanesthetized dogs and determined the oxygen saturation and tension in the first 0.15 ml of blood removed. The oxygen saturation of bone marrow blood is similar to that of blood drawn from the jugular vein. The oxygen contents and capacities, and the hematocrit values decrease to about the same extent in jugular and bone marrow blood after a 30 per cent hemorrhage, and recovery takes place at the same rate. Similar studies have been carried out on normal man and patients suffering from anemia and polycythemia vera (5, 102), and patients with primary and secondary polycythemia (59). The oxygen saturation of marrow blood was found to be similar to that of normal man; that of polycythemic individuals appears to be greater than normal.

The factors controlling the oxygen tension and oxygen supply to "erythrocytic nests" are not well understood. It is likely that the oxygen consumption of these growing cells is one consideration, and that the quantity and partial pressure of oxygen in the blood perfusing the area constitutes another factor. The bulk of marrow blood appears from histological evidence to be contained in the venous sinusoids. It seems reasonable to think that most of the mature erythrocytes found in the sample obtained by needle puncture are derived from the sinusoids. Presumably the erythrocytic nests are in diffusion equilibrium with the blood in the sinusoids even though the growing erythroid cells may be sealed off from the sinusoids as proposed by Doan (37, 38).

Intramedullary Pressure

The pressure within the medullary canal has been measured in various bones in different animals by a number of investigators. In animals, such as the dog and cat, it varies between 20 and 115, averaging some 50 mm Hg (8, 60, 74, 82). According to Petrakis (95), the pressures in the marrow of patients without marrow disease are uniformly low. Thus, in the sternum the pressures were approximately atmospheric, ranging from 2/0 to 17/15 mm Hg. Tocantins & O'Neill (106) report intramedullary pressures of 50 to 120 mm H₂O (3.7–8.9 mm Hg) in the human sternum. Petrakis (95) notes that human marrow pressures are lower than those seen in lower animals, and suggests that the difference may be attributed to the effects of anesthesia. The pressures measured in the region of the diaphysis are said to be definitely higher than those found near the epiphyses (fig. 5) (103).

Marrow pressure records show a definite, but small, pulse pressure (60, 74, 82, 103). This observation may be of practical importance, for Miles (90) reports that the absence of such fluctuations in pressure in the femoral head of patients indicates necrosis of this structure.

In addition to changes in pulse pressure, records of marrow pressure show rhythmic fluctuations corresponding to respiration (fig. 5) (60, 103). Also, slower rhythmic variations in pressure, presumably Traube-Hering waves, are sometimes seen (8).

Rasgone, Vater, and Marbarger (see 74) concluded that the marrow behaves as a semiclosed cavity and that changes in intramedullary pressure are dependent upon the volume of blood within the marrow cavity. When the venous return is obstructed, the mean pressure of the marrow increases and the pulse pres-

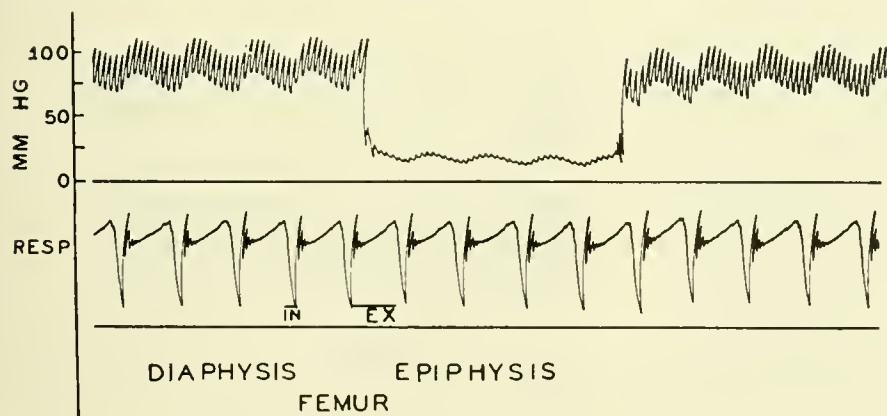


FIG. 5. Bone marrow pressure in diaphysis and epiphysis, and respiration rate recorded simultaneously in the dog. [From Stein (103).]

sure decreases (8, 103), whereas occlusion of the arterial supply to the bone decreases both mean and pulse pressures (8, 60, 103). Fracture of both sides of the femur causes the intramedullary pressure to fall to zero (8). Kalser and his co-workers (74) demonstrated a direct correlation between altitude and a fall in marrow pressure in dogs, and experimentally confirmed the fact that the marrow cavity acts as a semiclosed cavity.

This conception is supported by the study of Petrakis (95) who showed that the Valsalva maneuver in man produces a rise in systemic venous pressure, thus reducing the venous outflow from the marrow cavity and causing an increase in marrow pressure and a decrease in pulse pressure. Human marrow pressure varies with respiration and body position. Thus, sternal pressures were found to be near or below atmospheric pressures in recumbent, nonleukemic patients, and to vary with the respiration. The more distal iliac sites did not respond to the respiratory effects of forced breathing, but required the more strenuous effects of the Valsalva effort or of coughing to evoke changes. The higher pressures obtained in the iliac crest are presumably a result of the erect position of man. The effects of changes in body position and of alterations in respiration on marrow pressures indicate that, under conditions of normal activity, intramedullary pressure varies considerably and is passively affected by changes in venous pressure resulting from these activities.

In this connection, it is interesting to note that increasing the blood volume by the intravenous infusion of large quantities of saline causes a gradual increase of marrow pressure (8). On the other hand, a decrease in blood volume produced by hemorrhage causes a slow fall in medullary pressure (60).

Although marrow pressure does not ordinarily reflect changes in mean systemic arterial pressure (74), decapitated cats and cats with acute spinal injury have low femoral arterial pressures and do show low marrow pressures (60). Chronic "spinal" cats, in which the systemic pressure has returned to the levels seen before the spinal cord was cut, had bone marrow pressures similar to those found in unoperated animals. Stimulation of the cut peripheral end of either vagus nerve produced the usual slowing of the heart and fall in systemic pressure. This was associated with a reduction in bone marrow pressure. Changes in marrow pressure induced by stimulation of the central ends of the cut vagi or of the central end of the cut femoral or sciatic nerve, or by making an incision in the abdominal wall, were small and unpredictable. The

increase in systemic arterial pressure produced by occluding both carotid arteries was associated with a rise in marrow pressure.

Stimulation of the cut peripheral end of the abdominal sympathetic chain isolated from its connections with the spinal cord produced a fall in marrow pressure within the femur. A similar reduction in marrow pressure of the mandible occurs when the peripheral end of the cut cervical sympathetic cord is stimulated. The fall in marrow pressure caused by excitation of sympathetic nerve fibers has been used to trace the pathway by which such fibers reach specific bones (112).

To determine whether the sympathetic innervation of the marrow vessels is constantly influenced by tonic impulses, the abdominal sympathetic chain of one side was removed with strict aseptic precautions. Several days after recovery from the operation, simultaneous measurement of the marrow pressures showed no difference. However, when the experiment was repeated using cats made decerebrate by ligating both common carotid arteries and the basilar artery, the pressure in the denervated femur was found to be 25 mm Hg higher than its innervated control (60).

Stimulation of the peripheral end of the cut splanchnic nerve produced the usual prolonged rise in femoral arterial pressure, whereas the marrow pressure of the femur was greatly reduced (fig. 6) and recovered only as the systemic pressure returned to the control value (60). The same phenomena can be reproduced by the intravenous injection of Adrenalin (fig. 7) (8, 60, 82). The Adrenalin effect can be reversed by the prior injection of Hydergine (60). Other drugs which produce an increase in systemic pressure and a reduction in marrow pressure are norepinephrine (60), Pituitrin (8, 82), Neo-Synephrine (8), Synephrine (8), and tyramine (8).

A rise in systemic blood pressure with a simultaneous increase in marrow pressure is produced by the

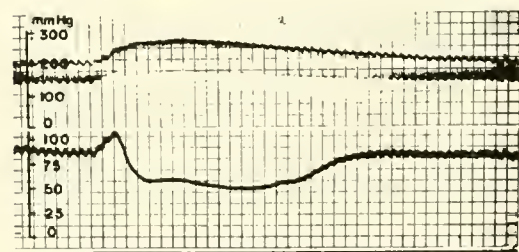


FIG. 6. Effect of stimulating the peripheral end of the cut splanchnic nerve on the femoral arterial pressure (upper record) and the marrow pressure (lower record) in the femur of the cat. [From Herzig & Root (60)]

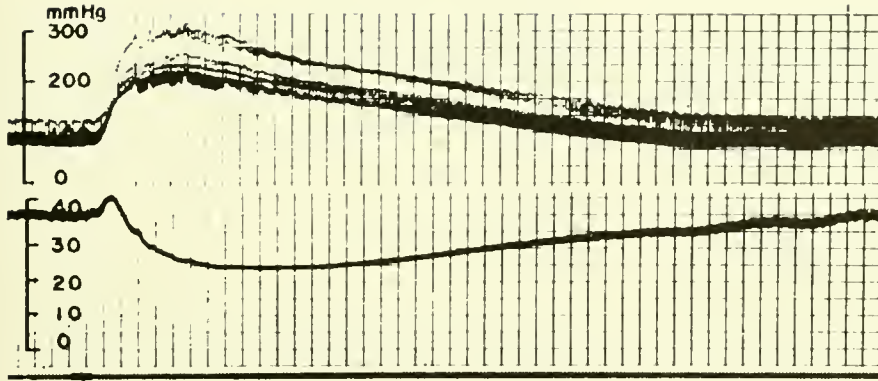


FIG. 7. Effect of injecting intravenously 1 ml of 1:50,000 Adrenalin on the femoral arterial pressure (upper record) and the marrow pressure (lower record) in the femur of the cat. [From Herzig & Root (60).]

administration of ephedrine (82), Benzedrine (8, 60), ergotamine tartrate (8) or nicotine (8). A reduction in both systemic and marrow pressure follows the injection of histamine (8, 82), acetylcholine (8), sodium nitrate (8), and amyl nitrite (60).

Patients with leukemia and multiple myeloma differ from nonleukemic patients in having elevated mean marrow pressures and increased pulse pressures (95). In patients with acute leukemia in whom the highest pressures are found, dicrotic notches are present in the pulse waves suggesting a lowered peripheral resistance in the marrow circulation. The degree of anemia could not be correlated with the mean pressures, nor with the pulse pressures in the marrow. The pressure data confirm the increased vascularity in the marrow in some forms of leukemia as demonstrated by the clearance of I^{131} from the marrow (94).

Temperature of Bone Marrow

This subject is of some importance, for it is generally believed that hematopoiesis requires the maintenance of a high bone marrow temperature (33). According to Huggins *et al.* (64), the more centrally placed bones of the extremities, the cranial bones and the sternum in the rat, rabbit, and pigeon have temperatures similar to that of the peritoneal cavity, whereas the temperature of the peripheral bone marrow of the extremities may be lower by 4 to 8 C or more. In adult man the red marrow is exclusively limited to the bones of the body trunk and head as well as the proximal portions of the limbs (92). Chemical activity of the marrow does not affect the thermal condition appreciably. On the other hand, the heat of muscular activity of the limbs increases marrow temperature.

Huggins & Blocksom (63) showed that an increase

in bone marrow temperature of the outlying bones led to the replacement of yellow by red marrow. They found a close correlation between the development of cellular marrow and a temperature level similar to that of the deep peritoneal cavity. However, they were uncertain whether this is a primary effect upon tissue metabolism, or a secondary vasomotor effect.

Petrakis (93), who studied the temperature in the sternum, iliac crest, tibia, spinous process, and vertebral body of ten patients, found temperatures ranging from that of the rectum in the vertebral body marrow, to 4 C below this in other bones. He interprets this to mean a lack of precise temperature regulation in hematopoietically active bone marrow. No correlation was found between temperature and cell type.

JOINTS

Gardner's excellent review (50) should be consulted for general information concerning the physiology of movable joints.

The Blood Supply

According to Davies (34) little has been added to the first description of the *circulus vasculosus* by William Hunter (66) who in 1743 wrote: "All around the neck of the bone there is a great number of Arteries and Veins which ramify into smaller Branches and communicate with one another by frequent Anastomoses like those of the mesentery. This might be called the *Circulus vasculosus*, the vascular border of the Joint."

At the articular margins, the capillaries form delicate anastomosing loops comparable in pattern with those seen in the mesentery. The blood supply of the synovial membrane and capsule communicate freely with the periosteal and epiphyseal supply; hence, the

shaft of the bone forms one nutritional unit, and the joint cavity and adjoining epiphysis form another. For this reason, Harris (35) uses the term *circulus vasculosus articuli et epiphyseos* to emphasize the nutritional interdependence of the joint and the epiphysis.

The venous drainage has received little attention. According to Testut (104), Sappey described the veins as characterized by frequent anastomoses, tortuosities, and varicosities. Testut remarks on their voluminous nature. Occasional valves are seen in the large veins, even in the more superficial parts of the synovial membranes.

The delicate nature of the synovial membrane and its blood supply is indicated by the fact that small extravasations of blood into the joint cavity are often found in animals, and some extravasation follows such a simple procedure as puncture of the joint (35).

The Nerve Supply

Chief among the features of the synovial membrane is its sensitivity to pain. Localization is often not highly accurate. To what degree the synovial membrane responds to other sensations, such as tension or pressure, is uncertain. Medullated and nonmedullated nerves entering the joint with the blood vessels form a plexus in the synovial membrane. The nonmedullated fibers in large part innervate the blood vessels and are probably of sympathetic origin. The effects of sympathectomy on the vascular supply of joints remains obscure, and in view of the paradoxical effects recorded by Engel (44) they need investigation. The synovial membrane shows an abundance of free nerve endings presumably subserving pain; end organs possibly concerned with proprioceptive impulses are variously described as Ruffini, Golgi, Mazzoni, looped or knotted types. Pacinian corpuscles are not a characteristic feature of the synovial membrane. Gardner (49) failed to find them, and Davies (34) confirms this.

Blood Flow Through Joints

Attempts have been made to determine the blood flow through joints by measuring the intra-articular temperature (61), by the application of the plethysmograph to a knee segment (9), by using a bubble flowmeter (25), and by means of an electromagnetic flowmeter (26, 27).

In adult anesthetized dogs weighing 9.5 to 31 kg, the blood flow through the knee joint amounts to 1.5 to 7.0 ml per min (26). The temperature of the joint must be markedly raised to obtain a measurable in-

crease in flow, changes of 10 C having little effect. Even a high external temperature of 60 to 65 C increases the blood flow only 15 to 57 per cent. Rapid cooling of the joint with ice packs causes the flow to decrease and remain fairly constant at half that of the control. However, sometimes the flow falls, rises, and then falls again; this is a type of behavior also described for skin vessels exposed to low temperatures (84). Removal of the ice packs is followed by a slow return of blood flow to the control level, partly owing to the delay in returning to the normal temperature. Nevertheless, a delay in the return of blood flow also occurs when the joint is quickly restored to the control temperature.

According to Horvath & Hollander (61), joint blood vessels dilate in response to cold and constrict when exposed to heat. This finding is not supported by the work of Hunter & Whillams (67) who used the same technique. The latter found that joint temperature fell when their subject was exposed to cold, and this they attributed to a reflex superficial vasodilatation resulting in a short period of excessive heat loss. On the other hand, Cobbold & Lewis (26) believe the decrease in intra-articular temperature on exposure to cold is the result of the constriction of joint vessels. In their plethysmographic study of blood flow through the knee segment, Bonney *et al.* (9) found that cooling the area resulted in a decrease in blood flow, and heating produced the reverse effect. Since they found a similar decrease in flow when the circulation to the skin of the segment was suppressed by Adrenalin iontophoresis, and further observed that after this procedure cooling no longer decreased the blood flow, Bonney *et al.* suggest that a different reaction to cooling may occur in articular than does in superficial vessels. The direct measurement of flow by Cobbold & Lewis (26) does not support this view. These investigators believe that the results reported by Bonney *et al.* are complicated by the presence of other tissue such as muscle.

Nervous Control of Joint Blood Vessels

The innervation of joints has been fully reviewed by Gardner (50). The blood vessels of the knee joint receive vasoconstrictor fibers by way of the articular nerves. Section of these increases blood flow some 50 per cent above the resting level (27). Stimulation of the peripheral cut end of this nerve produces vasoconstriction and a decreased blood flow. When the carotid arteries were occluded below the carotid sinus, the usual increase in systemic pressure was seen, but

no change in outflow from the joint was observed. Repetition of carotid occlusion after sympathectomy always produced an increase in flow. Lowering of systemic pressure by hemorrhage results in a decrease in joint blood flow which may cease if the blood loss is great enough.

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Dynamics of the pulmonary circulation

ALFRED P. FISHMAN

*Department of Medicine, Columbia University,
College of Physicians and Surgeons, New York City*

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THE PULMONARY CIRCULATION is part of an elaborate tonometric system for external respiration; it exists for the perfusion of the lungs rather than for their nutrition. And, as a consequence of its anatomical disposition with respect to the pulmonary airways and air spaces, the lung operates as a respiratory organ rather than as an air sac.

The lung appeared in the vertebrate phylum. In principle, it is designed to bring a thin stream of venous blood into gaseous equilibrium with a large volume of alveolar gas; however, in construction and in efficiency, it varies from class to class. Thus, in the amphibia—vertebrates which bridge the gap between the water and the land—the lung resembles a large bulla (fig. 1); this inefficient construction apparently suffices for the low metabolic requirements of the amphibia for oxygen. At the other extreme is the complex lung of the large and vigorous terrestrial vertebrates; in such a lung, septation and alveolation have created a porous structure, composed mainly of myriads of microscopic air spaces; suspended in the walls of these tiny air spaces are the pulmonary capillaries to which the pulmonary arterial tree delivers the entire right ventricular output for arterialization

(242). By this arrangement, the lung is equipped to operate efficiently over a wide range of metabolic activities: the enormous expanse of alveolar-capillary surface is capable of increasing during activity (346) and the geometric distribution of airways and blood vessels favors the continued balance of alveolar ventilation and pulmonary capillary perfusion even during strenuous exertion (7). Finally, governing the coordinated performance of this respiratory apparatus is a complicated system of ventilatory and circulatory controls; these succeed, despite the phasic and asynchronous nature of the ventilation and circulation, in stabilizing the gaseous composition of the alveolar gas and in ensuring adequate perfusion of the gas-exchanging surfaces.

In addition to participating in external respiration, the pulmonary circulation also performs several mechanical functions as a consequence of its architecture and location. Thus, as the bridge between the two sides of the heart, it is in a position to serve as a reservoir of blood for the left ventricle and to control left ventricular output by varying the pulmonary venous return (183). Similarly, as a consequence of their position at the outlet of the right ventricle, the smaller pulmonary vessels constitute a filter for systemic venous particles of all kinds, including the normal formed elements of the blood (1).



FIG. 1. Alveolar structure of the frog lung. Each lung consists of a large central cavity surrounded by numerous small chambers of varying size. The alveolar walls are outlined by the vessels which they contain. (Prepared in collaboration with H. O. Heinemann.)

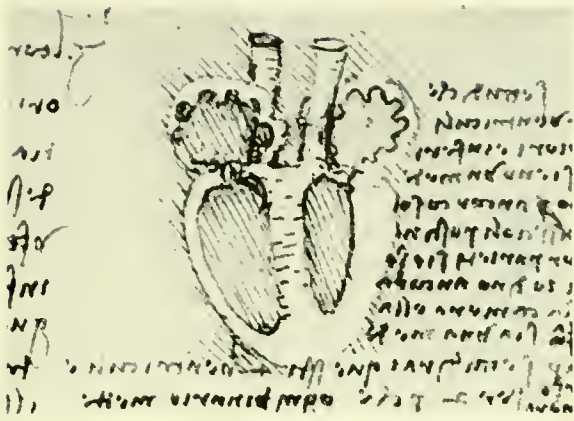


FIG. 2. Structure of the heart according to Leonardo da Vinci (98). The diagram shows the (nonexistent) pores in the ventricular septum, an essential component of the Galenical concept of the motion of the blood.

In recent years, the biological role of the pulmonary circulation and lungs has been emphasized (294). For example, the pulmonary vascular endothelium seems to contribute enzymes, such as lipoprotein lipases, to the perfusing blood (1). Mast cells, which are abundant in the lungs of many species, are believed to add a wide variety of substances, including heparin, histamine, hyaluronic acid, and serotonin (230). Finally, the walls of the pulmonary blood vessels and pulmonary tissue may also neutralize certain endogenous substances (e.g., serotonin) which could exert noxious effects if they gained access to the left heart and systemic circulation (158).

THE GROWTH OF IDEAS

The large pulmonary vessels were known to Herophilus of Alexandria in the fourth century, B.C. (228). But not until the time of Harvey (1578–1667) did dispassionate evidence begin to establish the structure and function of the pulmonary circulation (90, 91, 179). For convenience, the origins and growth of the modern ideas will be sketched under four separate headings: *a*) the appreciation and proof that the pulmonary vascular tree constitutes a closed circuit between the right and left hearts, *b*) the awareness that the lungs are concerned with external respiration, *c*) the systematic analysis of pulmonary hemodynamics, and *d*) the coordinated description of alveolar-capillary gas exchange. While such a presentation of the growth of ideas has the advantage of brevity, its lack of historical detail ignores foretellers

such as Ibn Nafis (291), Servetus (91), and Mayow (144), whose clairvoyance could only be appreciated retrospectively; it also exaggerates the contributions of the “finishers,” whose discoveries crowned the concepts and efforts of others.

Bridge Between Two Ventricles

In Harvey's time, Galenical misconception (fig. 2) and philosophic speculation still predominated. Although some of Harvey's predecessors and contemporaries had realized that there were no ventricular pores by which right ventricular blood could bypass the lungs and that the pulmonary artery was too large to serve only as a nutrient vessel, their preoccupation with the idea of the vascular system as the generator of essential spirits blinded them to the motion of the blood in the vessels. For Harvey, the idea of the pulmonary circulation as a bridge between the two ventricles was an essential component of his theory of the unidirectional circulation of the blood; he verified his theory by direct experiment and proposed “porosities” as the final links between the arteries and veins (195). In 1661, a few years after Harvey's death, Malpighi provided the final proof of pulmonary vascular continuity by visualizing the passage of blood from the pulmonary arteries to the veins by way of the pulmonary capillaries (280).

Role in External Respiration

Harvey was concerned solely with the mechanical aspects of the circulation of the blood. His concept did not deal with the prevalent notions about the role of the lungs either as a source of material for the generation of the vital spirit or as a refrigerating device to control the innate heat of the heart (166). Two years after Harvey's death, Lower (fig. 3), using Hooke's new respiration pump, showed that blood became arterialized as it passed from the right to the left side of the heart (172). The idea that ingredients of air, rather than air itself, were the basis of external respiration had to await new developments in chemistry and in physics. A century was to pass before: *a*) Black (1788–1867), Lavoisier (1743–1794), and Rutherford (1753–1814) identified the three respiratory gases; *b*) Lavoisier proved that oxygen rather than air was essential for life; and *c*) Lavoisier and Laplace likened respiration to combustion (90, 91, 144). Indeed, not until the mid-nineteenth century was it appreciated that combustion occurred in the tissues rather than in the lungs and that hemoglobin



FIG. 3. Richard Lower (1631–1691). In his book, *Tractatus De Corde*, he described his experiments with Hooke's respiration pump. These experiments proved that venous blood becomes arterialized in traversing the lungs and that blood absorbs a vital chemical substance from the air (172).

was involved in the transport of oxygen from the lungs to the tissues (90a, 144).

Analysis of Pulmonary Hemodynamics

Although certain aspects of the regulation of the pulmonary circulation—such as the influence of the respiration—were under experimental scrutiny by the middle of the eighteenth century (180), the systematic study of pulmonary hemodynamics could not begin without practical methods for measuring pulmonary vascular blood pressures and flow (189, 433). These became available about a century later: pulmonary arterial pressures were first measured in the laboratory of Carl Ludwig (fig. 4) in the 1850's, by using the recording mercury manometer in open-chest dogs (27); shortly thereafter, more elaborate measurements were made in the intact horse (90a, 91). In 1870, A. Fick (fig. 4) pointed out how measurements of respiratory gas exchange could be used to calculate the volume rate of pulmonary blood flow (130). But, without ready access to mixed venous blood, the direct Fick principle offered little promise of becoming a popular method for measuring the pulmonary blood flow in either the intact animal or man.

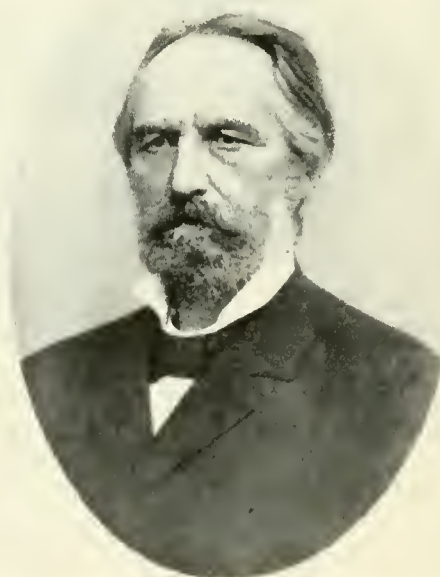


FIG. 4. Pioneers in hemodynamic measurements. *Left:* Carl Ludwig (1816–1895) introduced graphic recording of blood pressure in 1847. *Right:* Adolph Fick (1829–1901), student of Ludwig, in 1870 described the use of respiratory gas exchange for the measurement of cardiac output in intact animal or man. [After Rothschild (361).]

During the next seventy years, a wide variety of ingenious experimental preparations and new techniques were used to gain information about the remote pulmonary circulation: *a*) artificial experimental conditions were devised to control some respiratory and circulatory parameters so that others could be measured (40, 157); *b*) high-fidelity manometric systems were invented and used to register the details of the pulmonary vascular pressure pulses (183); *c*) cannulae were placed during open thoracotomy so that pulmonary arteriovenous pressure gradients could be measured in the closed-chest animal immediately after operation (225); *d*) angiostomy cannulae were devised so that pulmonary vascular blood pressures could be recorded at will in intact, unanesthetized animals (183, 187); and *e*) indirect methods were developed for the estimation of the pulmonary blood flow in intact animals or man (see Chapter 17).

This three-quarters of a century of steady progress underwent sudden acceleration in the 1930's. In 1929, Forssmann demonstrated on himself that a catheter could be safely threaded by way of a peripheral vein into the right heart (142); shortly thereafter, Klein measured the pulmonary blood flow by the direct Fick principle in man (90a). By World War II, the stage was set for Cournand, Richards, and their co-workers to begin their systematic studies of the pulmonary circulation in man under natural conditions (92). And, since the 1940's, right heart catheterization has been used for the sampling of mixed venous blood, for the injection of contrast material and test substances into the pulmonary circulation, and for the recording of blood pressures from the right side of the heart; the technique has also provided access to the venous effluent from special organs and regions of the body and has led to the techniques of left heart catheterization.

Alveolar-Capillary Gas Exchange

As indicated previously, the pulmonary circulation is predominantly built for alveolar-capillary gas exchange. Up to the turn of the present century, the precise nature of alveolar-capillary gas exchange was unclear; particularly uncertain was the mechanism by which oxygen traversed the alveolar-capillary interfaces: some held that oxygen was secreted by the alveoli (177); others maintained that diffusion alone was involved (10). The issue was finally settled in favor of diffusion by August and Marie Krogh (243). These studies by the Kroghs also paved the way for

measuring the rate of pulmonary capillary blood flow using soluble, inert gases as tracer substances (343).

To complete the picture of the coordinated circulatory-respiratory mechanism for external gas exchange (fig. 5), more had to be learned of the physiological behavior and of the physicochemical properties of the blood. To this end, Barcroft (fig. 6) provided precise experimental information concerning the dissociation of oxyhemoglobin (9); L. J. Henderson (fig. 6) and his collaborators analyzed blood as a physicochemical system and defined its role in the exchange of the respiratory gases between the atmosphere and the tissues (201, 297).

The regulation of alveolar-capillary gas exchange came under serious experimental scrutiny in the 1940's. In 1946, Euler & Liljestrand (125) proposed that the local concentration of the respiratory gases within the lung—a function of local ventilation-perfusion relationships—might regulate, in turn, the distribution of the pulmonary blood flow; the many experiments subsequently performed by others to test this hypothesis (132) will be considered later in this chapter. Interest in alveolar-capillary gas exchange was also stimulated in the 1940's from another direction, i.e., from the practical exigencies of aviation medicine in World War II; from this practical interest developed theoretical models, quantitative formulations, and graphic representations which have not only helped to resolve old problems in alveolar-capillary gas exchange but also to point up new ones (267, 327, 345).

COMPARATIVE PHYSIOLOGY

There are exceedingly few hemodynamic measurements in the nonmammalian vertebrates. In the fishes and sharks, the mean blood pressure in the ventral aorta (to the gills) is of the order of 30 mm Hg; as blood traverses the gills, blood pressure drops to reach a slightly lower level in the dorsal (systemic) aorta (57).

This arrangement of the circulation in the fishes is unfavorable for the systemic circulation. The hemodynamic situation of the systemic circulation begins to improve in the Amphibia and Reptilia in which the pulmonary artery is separate from the aorta and overrides a functionally single ventricle. Among the Reptilia, pulmonary arterial blood pressures have been measured in the turtle (352) and in the snake (222). In both of these species, the patterns of blood

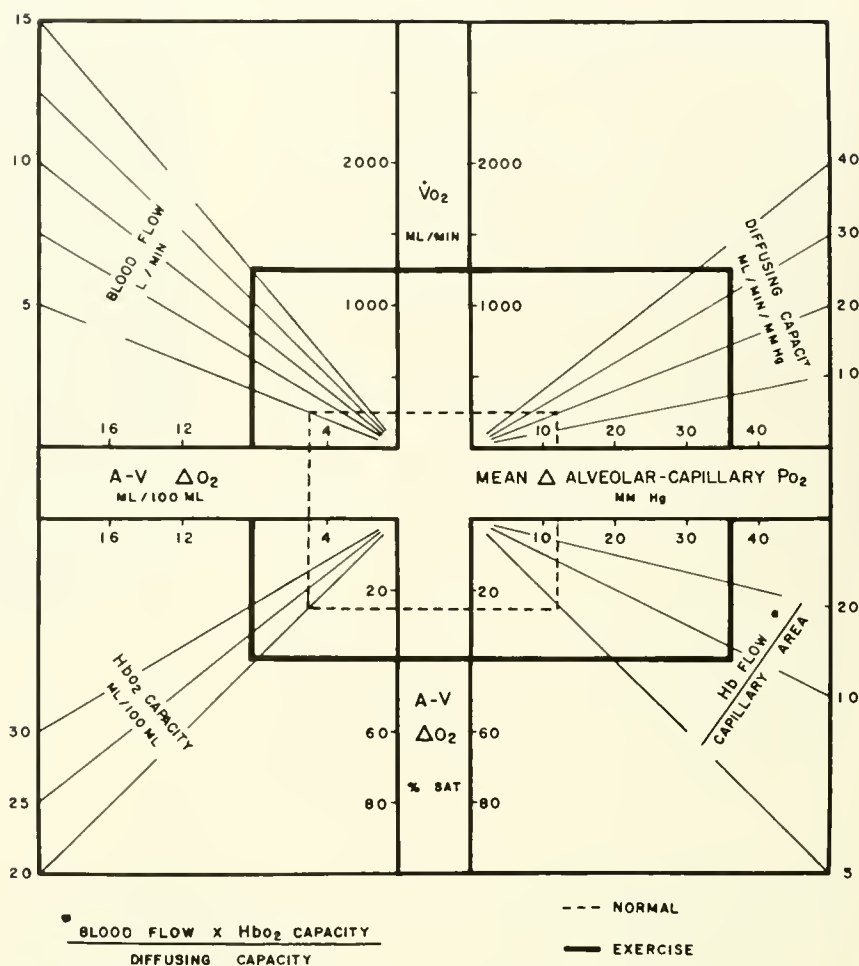


FIG. 5. Nomogram illustrating the respiratory and circulatory interplay involved in delivering an adequate supply of oxygen to the arterial blood. The dashed-line rectangle represents the situation at rest; the solid-line rectangle represents the situation during exercise. At rest, this subject has an oxygen requirement (\dot{V}_{O_2}) of 250 ml/min. Starting in the left upper quadrant, and moving from quadrant to quadrant in a counterclockwise direction, \dot{V}_{O_2} is shown to be met by a cardiac output of 5 liters/min, an oxygen capacity of 20 ml/100 ml, a Hb flow/capillary area of 5 and a diffusing capacity of 20 ml/min/mm Hg. Also pictured are the corresponding arteriovenous differences in oxygen content and saturation of blood (A-V ΔO_2), as well as the mean alveolar-capillary diffusing gradient for oxygen (mean Δ alveolar-capillary P_{O_2}). During exercise, as the oxygen requirement increases ($\dot{V}_{O_2} = 1250$ ml/min), these variables undergo appropriate change. A similar nomogram could be constructed for oxygen uptake in the tissues. [Based on Barcroft (9) and Lilienthal *et al.* (266).]

pressure are qualitatively similar: the systolic pressures in the pulmonary and systemic circulations are identical; the pulmonary arterial diastolic pressure is lower than the systemic arterial diastolic pressure, due to the presence of a spiral valve between the systemic artery and the ventricle (352). In the turtle, the pulmonary arterial pressure is of the order of 35/12 (352). When systemic vascular resistance increases, blood is diverted through the ventricular septal defect to the pulmonary circulation (443).

The ventricular septum is complete and the two circulations are entirely separate in the homeothermic mammals and birds. Among the mammals and birds, pulmonary arterial pressures have been measured in a wide variety of species including man, dog, cat, guinea pig (114), chicken (352), and calf (199). In the chicken and calf, the pulmonary arterial pressure is generally of the same order of magnitude as in the dog, cat, and man, i.e., of the order of 20 to 30 mm Hg systolic and 10 to 12 mm Hg diastolic; in the



FIG. 6. Joseph Barcroft (1872–1947) (*left*) and Lawrence J. Henderson (1878–1942) (*right*) photographed in September 1936. (Courtesy of D. B. Dill.)

guinea pig, it is somewhat lower (114), whereas in the pig, horse, cow, and steer it is often considerably higher (112, 199).

The pulmonary blood flow has also been measured in various conventional and unconventional laboratory animals including the goat (10), the horse (446), and the cow (112, 199). Although, in general, the larger species have the larger pulmonary blood flows, there is no consistent interspecies relationship between pulmonary blood flow on the one hand and either body surface area or weight on the other (22). Whether the disparities represent real biological differences, or the inadequacies of weight and body surface area as standards of reference, or artifacts arising from trying experimental situations, remains to be decided.

EXPERIMENTAL ANIMALS AND TEST PREPARATIONS

The normal pulmonary circulation has only been studied in a few dogs and humans. Instead, most of the observations have been made on the pulmonary circulations of anesthetized animals, of artificial preparations, and of patients with heart and lung disease.

Each of these three categories is a major deviation from normal: the use of anesthetized animals succeeds admirably in excluding the elements of anxiety and cooperation; but its substitutes, instead, blunted

vasomotor responses and changing levels of metabolism, respiration, and circulation (257). Artificial preparations, such as isolated vascular rings or isolated lungs, certainly allow remarkable control of mechanical parameters and may uncover influences which are obscured in the intact organism; but, by severing nervous connections, by failing to pass pulmonary blood through other vital organs, and by depending on abnormal perfusates, impaired nutrient circulations, deteriorating heart and lungs, and abnormal gas exchange, they may introduce not only discernible—but also hidden—artifacts (95, 141, 183). Finally, while the study of patients with heart and lung disease may be revealing to physicians who are attempting to gain insights into the mechanism of heart strain and failure, the results from these “experiments of nature” can rarely be used to predict the behavior of the normal pulmonary circulation, since both heart and lung disease tend to exaggerate the influence of mechanical factors and to alter the structure of the pulmonary blood vessels.

“Species difference” is a standard apology for atypical responses of the pulmonary circulation to diverse stimuli (95). Occasionally, the basis for this excuse is a distinctive morphological characteristic (72, 171, 199). For example, the small muscular pulmonary arteries of the rabbit contain much thicker media than do the corresponding vessels of rat, cat, and man (fig. 7). It is easy to imagine that contraction of such hypertrophied muscle could evoke the “gnarly” distortion of the rabbit’s vascular tree which follows the infusion of large quantities of norepinephrine (61); on the other hand, it is somewhat more difficult to imagine such an intense vascular response in species with muscle-poor precapillary vessels.

Species difference may reside in physiological as well as in anatomical peculiarities (218). For example, the rabbit is notoriously vagotonic, whereas the cat, dog, and man are generally regarded as sympathotonic; moreover, the pulmonary circulation of the rabbit also appears to be more susceptible to the effects of pharmacological agents, such as histamine, than is the pulmonary circulation of the dog (442). Such anatomical and physiological peculiarities occur throughout the animal kingdom, complicating the transfer of information from one species to another (95, 239, 352).

FUNCTIONAL ANATOMY

The dependent position of the pulmonary circulation—within the lung and thorax on the one hand,

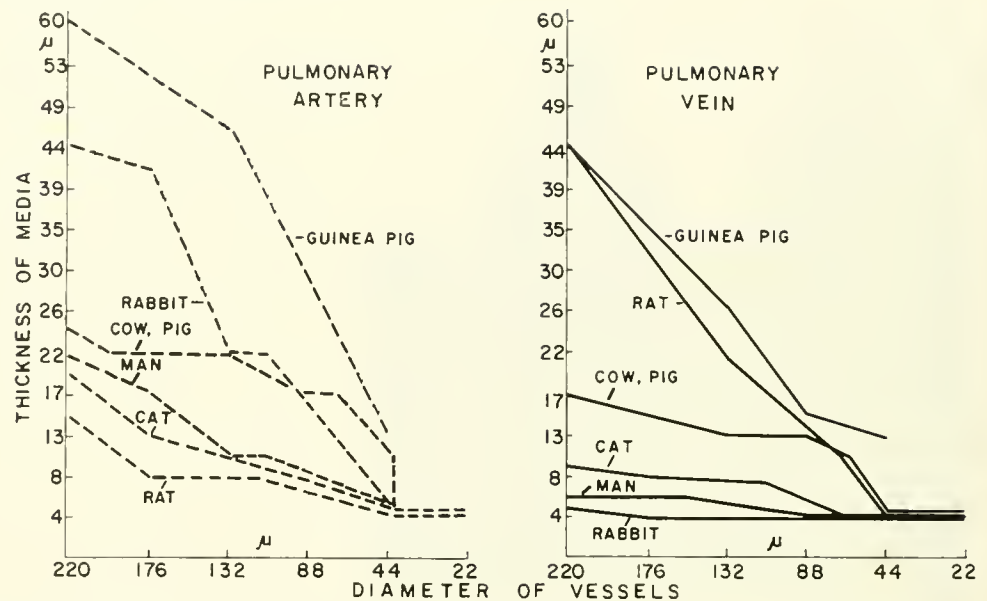


FIG. 7. Relationship between vascular calibers and medial thickness in different species. Both the small pulmonary arteries and the small pulmonary veins are well developed in the guinea pig, cat, calf, and pig. On the other hand, in man and in the rabbit, only the arterial muscle, and in the rat only the venous muscle, is well developed. [Redrawn after Takino (392).]

and between the two ventricles on the other—subjects it to a variety of mechanical influences. Consequently, the following appraisal of the functional anatomy of the pulmonary circulation will take into account not only those features of the vascular tree which determine pulmonary vascular distensibility and resistance to perfusion but also the extravascular structures which may, under appropriate conditions, modify or obscure the natural properties of the pulmonary vessels (288).

Unless expressly indicated, the anatomical descriptions which follow derive largely from the examination of the lungs of normal man at sea level. It is likely that, in most respects, the generalizations about structure, and particularly about the relationships between structure and function, apply almost as well to the cat and to the dog. However, much more has to be learned before the generalizations from normal man at sea level can be applied directly either to other test animals, such as the rabbit and the cow, or to normal native residents at high altitudes, or to sea level residents with abnormal pulmonary vessels or parenchyma (99, 392).

Blood Vessels

OVERLAP OF DISTENSIBILITY AND RESISTANCE CHARACTERISTICS. In the systemic circulation, the term

“arteriole” is synonymous with “resistance” vessel. Characteristically, the systemic arteriole has a heavy coat of circular smooth muscle and a high ratio of wall thickness to lumen diameter. With respect to size, “systemic arteriole” generally refers to vessels of 300 to 400 μ or less, depending on the organ in which they are found (50). On the other hand, in the low-pressure pulmonary circulation, the anatomical counterpart of the systemic arteriole does not exist. This lack of sphincteric precapillary vessels has several implications: *a*) that other small vessels may contribute appreciably to the pressure drop between the pulmonary artery and veins; *b*) that the small pulmonary vessels may also serve as storage vessels, changing caliber passively with the pulmonary blood volume; and *c*) that under appropriate conditions, each of the small vascular segments may constitute the dominant pulmonary vascular resistance to blood flow.

LARGE PULMONARY VESSELS. The pulmonary artery rapidly subdivides into terminal branches which have thinner walls and wider bores than the corresponding branches of the systemic arterial tree. The media of the main pulmonary artery is about half as thick as that of the aorta; the elastic fibers are short and far less orderly than in the aorta (198). The smooth muscle appears to insert on the elastic

fibers, suggesting an arrangement capable of controlling either the pressure of the wall on its contents or the volume of blood contained within the large vessel (198). In general, the structure of the large vessels seems better suited for varying their distensibility than their geometry; nonetheless, the possibility exists that constriction of large vessels may also effect pulmonary vascular resistance to blood flow (126).

In the normal human lung the pulmonary arteries are end-arteries, continuing without branching to the level of the first alveoli in the walls of the respiratory bronchioles (292, 421). Unfortunately, too little is known of the pattern of branching to serve as a reliable basis for predicting the distribution of resistance along the length of the pulmonary vascular tree (140, 169, 205). The arterial portion of the pulmonary circulation lies adjacent to the bronchial tree; indeed, in the region of the respiratory bronchiole, arterial bifurcations straddle the airway (117). Consequently, the arterial branches are more susceptible to passive distortion by the conducting airways than are the venous branches which are situated at the periphery of the lobule.

The pulmonary veins are end-veins (421). Their musculo-elastic components are more irregularly dispersed than those of the corresponding pulmonary arteries; their media contain more collagenous fibers. At the entry of the veins into the left atrium, extensions of cardiac muscle become incorporated into the venous walls. The suggestion has been made that under certain experimental conditions, these muscular extensions may act as "throbbles" (56, 121, 392, 394).

SMALL MUSCULAR PULMONARY VESSELS. From the point of view of vasomotor activity, three concepts are generally held: 1) vascular smooth muscle is prerequisite for active change in caliber; 2) during a change in vasomotor tone, the small, muscle-containing vessels are the site of changed resistance; and 3) the thicker the media, the more apt is the vessel to constrict, the less apt is it to undergo passive dilation, and the more likely is it to offer appreciable resistance to perfusion (59, 141).

The anatomical characteristics of the small muscular pulmonary vessels are illustrated in figure 8. The upper half of this figure depicts the structure of exceedingly small ($30\ \mu$) pulmonary vessels: in neither the pulmonary "arteriole" or venule is smooth muscle discernible; by way of contrast, the coat of smooth muscle in the systemic arterioles is readily apparent. The lower half of this figure contrasts a small pulmonary artery and a small pulmonary

vein—each about $50\ \mu$ in diameter—with a systemic arteriole of approximately the same size; pulmonary arterioles of this size are to be found at the level of the alveolar ducts and alveoli, buried in pulmonary tissue (118). It may be seen that the pulmonary arteriole contains only a thin rim of smooth muscle; in the corresponding pulmonary venule of $55\ \mu$, no smooth muscle can be recognized; on the other hand, the systemic arteriole contains a thick media. It is difficult to imagine the pulmonary vessels shown in figure 8 as the sites of intense vasoconstriction.

Somewhat better suited for vasomotor activity are the larger precapillary vessels. These "small muscular arteries" range from 100 to 1000 μ in diameter (403), contain well-formed media, and lie adjacent to the respiratory bronchioles. They are usually separated from the pulmonary tissue by perivascular lymph spaces and their muscular coats thin as they proceed peripherally to the vicinity of the alveolar ducts. From these muscular vessels, the pulmonary arterioles generally arise at right angles so that the configuration of muscle at their origins often appears sphincteric (118, 196).

The corresponding venules of 100 to 1000 μ lie at the periphery of the lobule. And, in contrast to the small muscular arteries, smooth muscle is either poorly organized or absent and the elastic fibers are irregular and indistinct. Consequently, even pulmonary veins up to 1000 μ in diameter seem to be poorly equipped for vasomotor activity.

CAPILLARIES. At the alveolar border, the precapillary vessel subdivides to form a racemosing network of capillary segments sandwiched between adjacent alveolar walls (fig. 9, insert) (292). Whether these capillaries lie free between the alveoli or indent them—a structural distinction relevant to estimates of pericapillary pressure—is uncertain.

The capillary circulation has certain distinctive features: a) each of these capillary segments is approximately 10 to 14 μ in length and 7 to 9 μ in diameter (422); b) except in congested lungs the red cells pass through in single file (fig. 9); c) the capillary networks in different parts of the lung differ with respect to the length, caliber, and number of constituent vessels (162, 292); d) "pores," presumed on physiological grounds to exist in the pulmonary capillary wall, have not been seen by electron microscopists; e) chemical analyses have failed to settle if the capillary wall is predominantly aqueous or lipid in nature (375); f) there appear to be neither contractile cells around the capillaries nor smooth

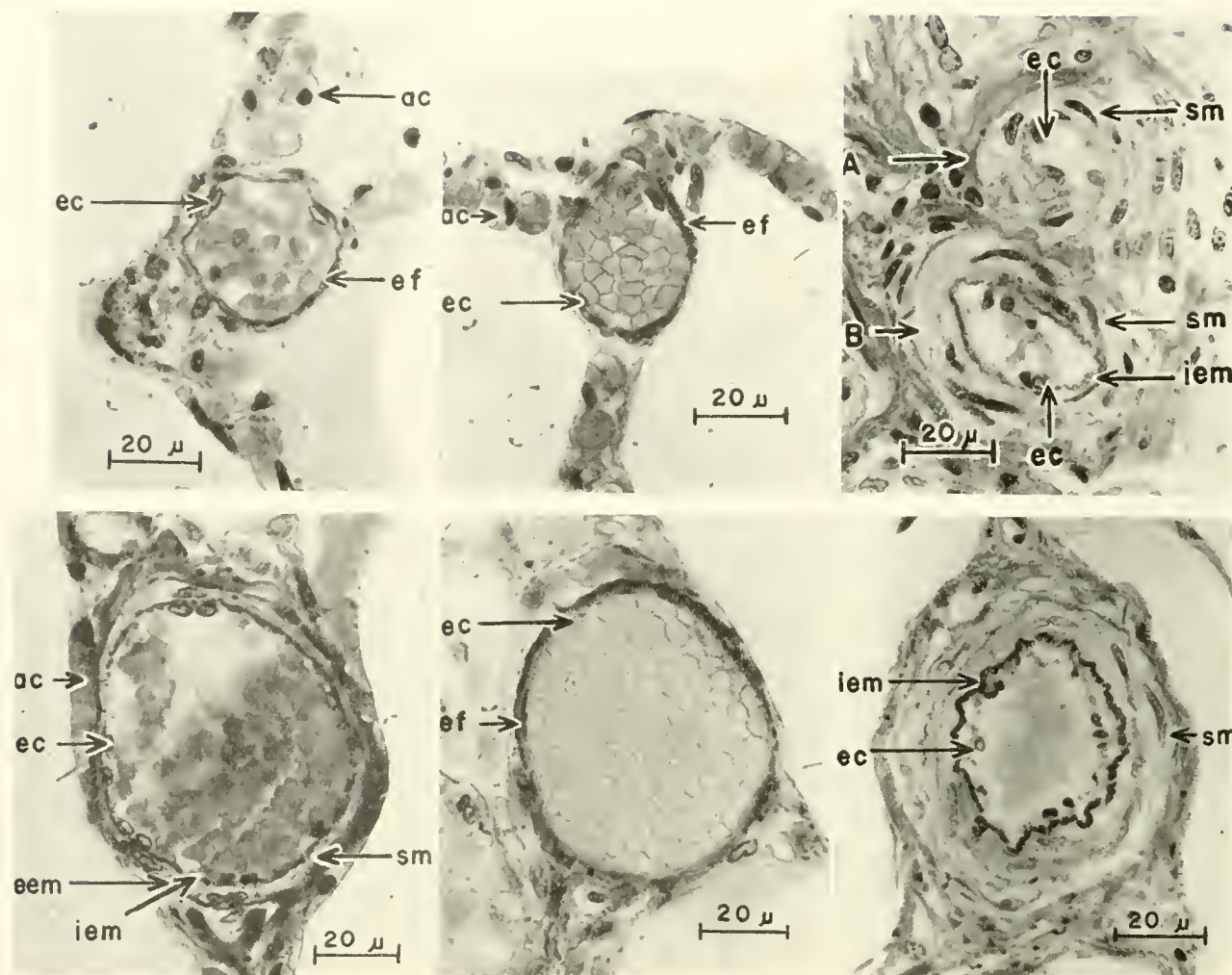


FIG. 8. Structure of small pre- and postcapillary vessels. *Upper half.* Comparison of a 30 μ pre-capillary vessel (*left*) and postcapillary vessel (*center*) with systemic arterial branches (*right*) of the same size. The pulmonary pre- and postcapillary vessels are structurally similar; they are strikingly different from the systemic arterial branches. *Lower half.* Comparison of a 57 μ pulmonary artery (*left*) and a corresponding pulmonary vein (*center*) with systemic arteriole (*right*) of the same size. Muscle cannot be identified in the vein. *ec*, endothelial cells; *ef*, elastic fibers; *sm*, smooth muscle; *iem*, internal elastic membrane; *eem*, external elastic membrane; *ac*, alveolar capillaries. (Elastic tissue stain. 585 \times .) [Courtesy of E. R. Weibel (132).]

muscle in the capillary walls. Without such contractile elements, it is unlikely that the capillaries can contract actively in the conventional manner of muscle-containing vessels (400); on the contrary, capillary lumens are more apt to be passively narrowed by swelling of endothelial cells, by perivascular transudates (114), by raised alveolar pressures (351), and by the pushes and pulls of adjacent structures (397).

According to Weibel, the "typical" alveolus in man is more like the cell of a honeycomb than a sphere (422). It measures approximately 200 to

250 μ in diameter. Each alveolus is lined by a continuous epithelium (40 to 65 $m\mu$ thick) which changes its submicroscopic appearance upon appropriate stimulation (276, 375). In the human lung approximately 300 million alveoli are juxtaposed to approximately the same number of capillary segments. After the age of 8 years, an increase in the size of the lung seems to involve an increase in the dimensions of existing alveolar-capillary units rather than in their number (422).

The thickness of the alveolar-capillary interface is of the order of 285 to 640 $m\mu$ (375): not all of the

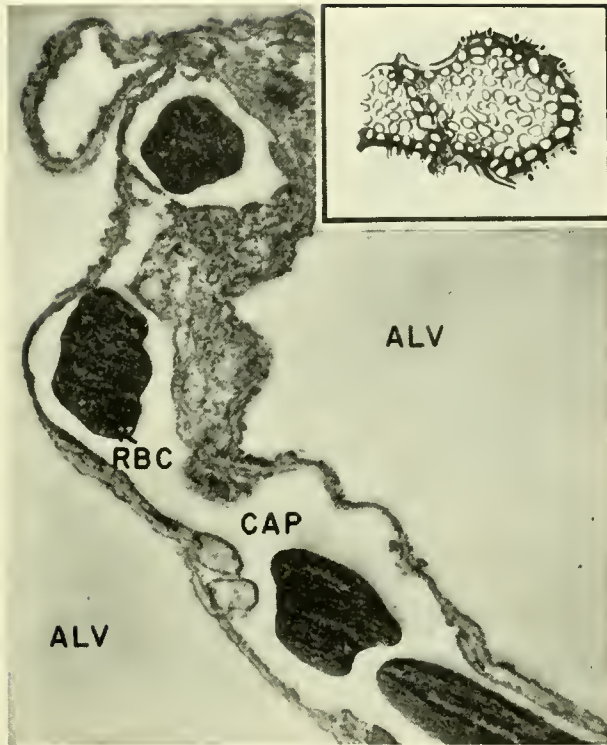


FIG. 9. Electron microphotograph of human lung. The red cells (RBC) are shown passing single file through a pulmonary capillary (CAP) between adjacent alveoli (ALV). 19,370 \times . [Courtesy of Dr. Councilman Morgan.] Insert: Network of capillaries in the walls of the sacculi alveolares. 330 \times . [From Miller (292).]

alveolar surface is ordinarily used for gas exchange; nor is all of the capillary circumference in contact with alveolar wall (196). The portion of the available capillary surface which is actually used appears to vary with the total lung volume, the degree of capillary filling and the size of the alveoli. At a volume corresponding to three-quarters of the total lung capacity, the capillary network occupies 60 per cent of the alveolar surface and the capillary blood volume is of the order of 200 to 250 cm^3 (422).

Over the years, anatomical measurements of the capillary surface area have provided exceedingly variable results: values have ranged from 50 m^2 to 140 m^2 (132). Some of this discrepancy is undoubtedly attributable to methodological differences (143), to the uncertainties of reconstructing the lung on the basis of small sections, and, particularly, to the failure to specify the lung volume at which the measurements were made. The recent measurements by Weibel indicate that at the resting position of the lung, the capillary surface is of the order of 50 to

70 m^2 ; at three-quarters of the total lung capacity it increases further (to the order of 90 m^2) (422).

Extravascular Smooth Muscle

Pulmonary smooth muscle is contained not only in the vessels but also in the tracheobronchial tree and in the pulmonary tissue. In man, the neatly organized tracheobronchial smooth muscle continues down to the mouths of the alveoli (fig. 10) where it is in a position to influence passively the pressure in the alveoli and, thereby, the caliber of the capillaries in the alveolar walls (8, 196). Although parenchymal smooth muscle is apparently plentiful in the amphibian and reptilian lung (220, 236), and in patients with chronic pulmonary disease (265), the quantity and arrangement of this parenchymal smooth muscle in the normal human lung is unknown. Nonetheless, because of its close association with the elastic network of the lung, parenchymal smooth muscle may conceivably affect vascular calibers directly by contiguity and, indirectly, by changing the pulmonary lung volume and distensibility. Moreover, since the musculo-elastic system of the lung is nourished by the bronchial arteries, the possibility exists that agents which reach the lungs by way of the systemic circulation may change pulmonary vascular dimensions through their effects on extravascular, rather than intravascular, smooth muscle.

Systemic Blood Supply of the Lung

In the normal human and canine lung, the bronchial arteries arise from intrathoracic systemic arteries and deliver oxygenated blood to the walls of the tracheobronchial tree, the supporting framework of the lungs and the walls of the pulmonary arteries and veins (133). Accordingly, they are nutrient arteries. In contrast to pulmonary arteries of equal caliber, the bronchial arterial walls are thick and their innervation is plentiful. In the normal lung, bronchial venous blood drains largely into the azygous veins but some also enters the pulmonary veins (263, 445).

The quantity of blood carried to the lungs by the bronchial arteries is difficult to measure precisely; the complexity of the problem may be inferred from the wide variety of experimental approaches which have been attempted in both dog and man (93, 133, 214, 368). Nonetheless, despite inevitable differences, the results of these diverse trials suggest that the bronchial arterial flow ordinarily constitutes only an

FIG. 10. Schematic representation of the disposition of smooth muscle in the terminal portions of the respiratory tree. The cut muscle appears as small nodular structures of various sizes and shapes; it ends at the mouths of the alveoli. [After Baltisberger (8).]



exceedingly small fraction of the cardiac output and that the effect of the bronchial circulation on the behavior of the normal pulmonary circulation is negligible. The evidence for the latter conclusion is of three general types: 1) the difficulty encountered by anatomists in finding bronchial-pulmonary arterial communications in the normal human or canine lung except by elaborate injection techniques (421); 2) the measurements in the dog during artificial perfusion of the lungs which indicate that the normal bronchial arterial flow is of the order of 1 to 2 per cent of the cardiac output (55, 423); and 3) the measurements in intact man which indicate that the normal bronchial arterial blood flow is too small to be measured by conventional techniques (139, 152). It should be noted that under some ex-

ceedingly artificial experimental circumstances, the bronchial circulation in the dog has been found to exert an appreciable hemodynamic effect on the pulmonary circulation (95). However, because of the unusual experimental conditions, these results seem to indicate the ultimate potential of the bronchial circulation rather than its actual performance in life.

The systemic blood supply of the lung undergoes a remarkable proliferation in various disorders of the heart and lungs (79, 98, 133, 263): old vessels enlarge and become tortuous; new vessels appear and join with the old to form bizarre Medusae patterns. Moreover, in contrast to the normal lung, in which precapillary communications between the two circulations are difficult to demonstrate (292, 420), the enlarged precapillary anastomoses between the

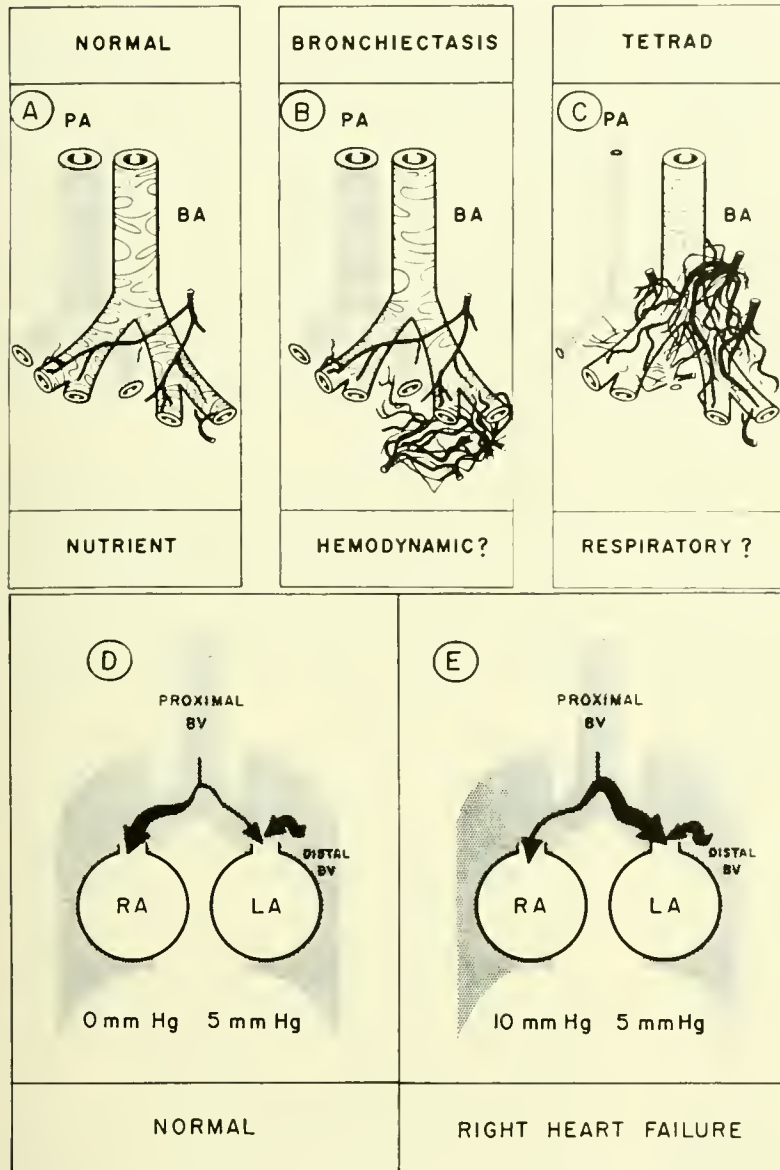


FIG. 11. Pulmonary collateral circulation. *Upper half*: The arterial portion. *A*: usual nutrient function; *B*: expansion to constitute a hemodynamic burden, as in diffuse suppurative disease; *C*: participation in external respiration when systemic arterial hypoxemia coexists with inadequate pulmonary arterial blood flow. *Lower half*: The venous portion. *D*: usual emptying of proximal bronchial veins; *E*: alternate emptying of proximal bronchial veins when right atrial pressures exceed left atrial pressures. [After Fishman (133).]

pulmonary and systemic circulations are grossly visible (264).

The proliferation generally does not affect the entire collateral circulation in a uniform manner (fig. 11). Thus, in the portion of the lung which lies adjacent to an area of pulmonary inflammation, as well as in the lung with a severely compromised pulmonary arterial blood supply, it is the arterial portion of the collateral circulation which expands; on the other hand, the venous portion of the collateral circulation undergoes the more striking expansion in certain types of pulmonary emphysema and in mitral stenosis (263). If the expanded collateral circulation becomes sufficiently large—as in diffuse suppurative

disease of the lung (263)—it may carry large volumes of blood, and transmit systemic blood pressures, to the point of constituting a hemodynamic burden on the pulmonary circulation.

It should be noted that as the collateral circulation proliferates, the difficulties in measuring the rate of collateral blood flow also grow. Particularly troublesome, from the technical point of view, are the multiple origins of the collateral arterial branches on the one hand and the alternate venous outlets on the other (fig. 11). Indeed, on account of this anatomical arrangement, it is difficult to measure volumetrically the total collateral blood flow even in the open-chest dog in which the heart and thoracic vessels are

exposed for cannulation. Another problem is the prediction, on a priori grounds, of the hemodynamic behavior, i.e., the blood flow, the driving pressure, and the resistance to perfusion of anastomotic channels which vary so in length, caliber and, possibly, in tone. However, one anatomical aspect of the expanded collateral arterial circulation does lend itself to physiological exploitation: the precapillary anastomoses make it possible to measure that part of the collateral arterial inflow which reaches the gas-exchanging surfaces of the lung and is available for respiratory gas exchange, i.e., the "effective" collateral blood flow (31, 139).

Venous Admixture

In the normal pulmonary circulation a small quantity of venous blood traverses anatomical channels to bypass the gas-exchanging surfaces of the lungs, thereby reducing the oxygen tension of peripheral arterial blood. This shunt has diverse anatomical origins: bronchial veins, anterior cardiac veins, Thebesian veins, portal veins, mediastinal veins and pulmonary arteries; in normal man and dog the volume of shunted blood is generally considered to be of the order of 2 per cent of the cardiac output (13, 23, 349).

In the rabbit and guinea pig, arteriovenous channels have been seen on the surface of the transilluminated lung (219). In the dog, the evidence for such shunts is less direct and there is considerable dispute concerning their size (349). Two types of observations favor a large size: 1) glass spheres, up to 500 μ in diameter, reach the left heart following injection into the pulmonary artery (322); 2) radiopaque material, forcefully injected through the side vent of a wedged pulmonary arterial catheter, traces a cine-angiographic course suggestive of short-circuits (331). Opposed is the experimental evidence that these channels are closer to 25 μ than to 500 μ in diameter (38, 167, 349). A reasonable interpretation of the disparate results in the dog is that the experimental conditions determine the degree of patency of these channels and that ordinarily these channels are virtually closed (95).

The situation is somewhat more tenuous for the human lung: on the one hand, large glass spheres (up to 500 μ in diameter) also traverse the isolated human lung (322); on the other, is the inability of painstaking histological examination to disclose the channels (421) and the failure of physiological measurements to obtain the high values for venous ad-

mixture which would be consistent with the presence of large, patent channels (23). If arteriovenous channels do exist in the normal human lung, they seem to allow very little blood flow under ordinary conditions.

The small anatomical shunt in the normal animal or man stands in marked contrast to the large size which it may achieve in certain clinical states, such as congenital right-to-left intracardiac shunts and pulmonary hemangiomatosis (155, 226). Appreciable shunting has also been demonstrated in those patients with cirrhosis of the liver who develop portal-pulmonary venous communications (63).

Pulmonary Vasomotor Nerves

There is no doubt about either the existence of pulmonary vasomotor nerves or their ability to change pulmonary vascular calibers when appropriately stimulated; only their physiological meaning can be questioned (96, 382).

The pulmonary vasomotor nerves have been most intensively studied in the dog: both vasodilator and vasoconstrictor fibers have been identified in the upper sympathetic chain and in the vagus nerves (95). Because of the complicated intermingling of these fibers—not only with each other but also with bronchial and cardiac fibers—electrical stimulation often fails to separate vagal from sympathetic effects on the one hand, and vasomotor from bronchomotor and cardiac effects on the other (95).

For comprehensive reviews of pulmonary and pulmonary vascular innervation the reader is referred elsewhere (96, 267). A few aspects are particularly relevant to considerations of pulmonary hemodynamics: *a*) the large pulmonary arteries and veins are more richly innervated than their smaller counterparts (81, 147, 392); *b*) the muscular arteries and arterioles are more richly innervated than the corresponding veins and venules (392); *c*) nerve endings reach the medial and subendothelial layers of the large arteries and veins (392); *d*) sensory nerves and receptors have been identified in the airways and in the large pulmonary arteries and veins (6, 80); *e*) the bronchial arteries are more richly innervated than any other pulmonary vessels (292); and *f*) the nerve supply to the bronchi exceeds that of the pulmonary vessels (392).

As a pharmacological device for estimating the concentration of adrenergic nerve endings in the different parts of the pulmonary vascular tree, Euler & Lishajko (126) compared the concentrations of norepinephrine in the central and in the peripheral

portions of the human pulmonary vascular tree. In keeping with the anatomical evidence for a predominant distribution of nerves to the larger pulmonary vessels, they found that the large pulmonary vessels (of the dog and cow) contain larger quantities of norepinephrine than do the small pulmonary vessels. The greater concentration of nerves in the region of the large pulmonary vessels is consistent with the notion that the pulmonary vascular bed is better innervated for tensing its large vessels than for shrinking the caliber of its small ones (403). However, this attractive idea, which is based on anatomical observations, is inconclusive on several accounts: *a*) the display of an abundant innervation provides no measure of either the number or the nature of the impulses which the nerves transmit; *b*) consecutive muscular segments of a single pulmonary vascular unit may be differently affected by a stimulus (95); and *c*) because of its mixed embryological origin in endoderm and mesoderm, pulmonary vascular innervation may possess subtle, and as yet undisclosed, features.

PULMONARY BLOOD FLOW

In subjects with a normal heart and circulation, the pulmonary blood flow, the pulmonary capillary blood flow and the output of each ventricle (the cardiac output) represent virtually identical quantities. In previous chapters of this book, the cardiac output is considered with respect to its measurement (Chapter 17) and control (Chapters 15 and 16); the present section will confine itself to resting measurements of pulmonary blood flow, leaving for subsequent sections the pulmonary capillary blood flow and the behavior of the cardiac output during exercise.

Normal Values

For the sake of comparison, cardiac output in man is generally expressed per square meter of body surface area (cardiac index): in one representative study, the average cardiac index of a group of basal, postprandial, supine human adults was 3.12 liters/min/m² (SD ± 0.40); the corresponding oxygen uptake of this group was 138 ml/min/m² SD ± 14 (87). Unfortunately, even in adults, body surface area is not an ideal standard of reference; it becomes even less reliable when subjects of different age, sex, and body build are compared, since the "normal"

values have been derived from a select portion of the adult population. In the unanesthetized dog, the cardiac output per minute is of the order of 150 ml per kg (12). It should be emphasized that there are exceedingly few such measurements on the unanesthetized dog and the values which do exist are far from consistent (303).

Excitement (discomfort or anxiety) may artificially increase the "basal" cardiac output. This fact has been illustrated by measurements on the unanesthetized dog prior to, and following, treadmill exercise: the resting cardiac output, while awaiting the start of treadmill exercise, was higher than the resting cardiac output after the exercise was finished (12). Excitement may continue to operate during the test periods. Fortunately, there are objective criteria which can be used to detect the existence of disturbing emotional influences; these include tachycardia, a high respiratory exchange ratio of the expired gas, a high oxygen uptake, and a high pH of systemic arterial blood (136). Transient episodes of emotional stress are apt to introduce appreciable errors into steady-state measurements of flow, particularly by the Fick principle (412, 439); on the other hand, sustained excitement will artificially increase the cardiac output. In the latter instance, the normality of the cardiac output can be appraised by comparison with the simultaneously measured oxygen uptake (fig. 12). Ordinarily, the arteriovenous difference for oxygen is of little help in such an appraisal since its variations at rest approximate the limits of analytic error (e.g., average of 38.4 SD ± 6.3 ml per liter (334)).

Uneven Pulmonary Blood Flow

The pattern of distribution of the right ventricular output throughout the lung has been examined in several different ways: *a*) direct inspection of the pulmonary blood vessels; *b*) fractional, or continuous, analysis of the alveolar component of expired air; *c*) bronchspirometry or regional sampling of alveolar air; *d*) external scintillation counting following the breathing of radioactive gases; and *e*) the use of conceptual models to explain actual respiratory gas exchange.

Direct inspection of the lung for the determination of the pattern of the pulmonary blood flow has been practiced for at least 90 years (54). Three types of observations have been made: 1) the examination of the surface of the exposed lung in the living animal (21, 105, 419), 2) the postmortem examination of the

excised lung following the injection of tracer materials (323, 405), and 3) roentgenography, including angiocardigraphy (202). These approaches are all qualitative but have clearly established two features of the pulmonary circulation: the distribution of the pulmonary blood flow is ordinarily quite uniform

but that it may be drastically modified by appropriate stimulation (fig. 13); structural abnormalities are prepotent over physiological influences in determining the course taken by the blood (427). The direct observations have also been used to account for a variety of otherwise inexplicable clinical phe-

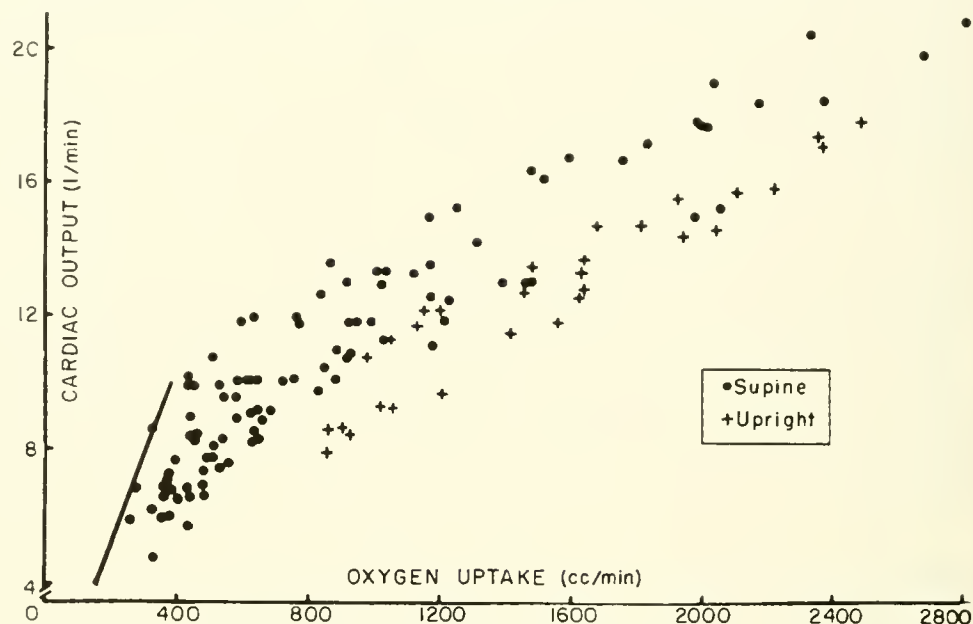


FIG. 12. Relationship between oxygen uptake and cardiac output at rest (supine), during supine exercise, and during upright exercise. The diagonal line (at the far left) is based on the method of least squares and represents spontaneous variations in the cardiac output in 56 normal subjects at rest. This line lies to the left of the exercise data and has a steeper slope. For any given oxygen uptake, the cardiac output is lower during upright exercise than during supine exercise. [After Reeves *et al.* (336).]

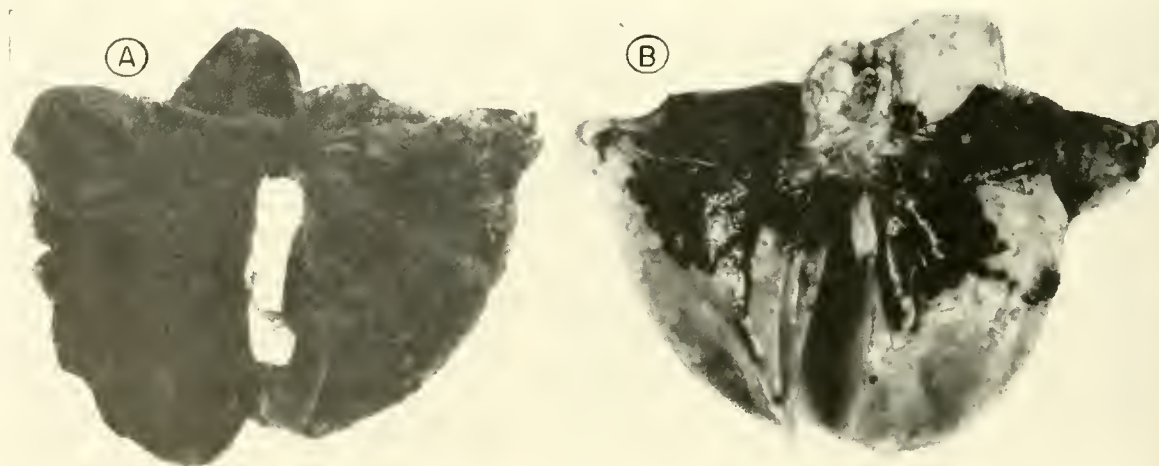


FIG. 13. Variations in the distribution of the pulmonary blood flow. For each experiment, filtered India ink was injected into a marginal ear vein of an unanesthetized rabbit loosely restrained in its normal body position. A: uniform distribution of the India ink; B: "patchy" distribution following introduction of a cardiac catheter into the right ventricle via the right external jugular vein (local procaine anesthesia). [After Tuller *et al.* (405).]

nomena, including the bizarre "butterfly" shadows of pulmonary edema (202) and the maintenance of the virtually normal oxygenation of peripheral arterial blood in patients with atelectasis and pneumonia (85).

Much more relevant to the performance of the lung in gas exchange is the distribution of the pulmonary capillary blood with respect to alveolar volume, alveolar ventilation, and pulmonary diffusing surfaces. In the normal lung, these parameters are ordinarily quite precisely balanced (131, 145, 427); in disease, the upsets may be quite striking (58). Two approaches are in popular use for relating pulmonary capillary perfusion to alveolar ventilation: the determination of the pattern of change in the alveolar composition of a respiratory gas (284) and of the respiratory exchange ratio (428) during a single expiration; the determination of the rate of increase in the peripheral arterial oxygen saturation (314) and tension (131) during oxygen breathing. It has been pointed out elsewhere that each of these approaches has its own uncertainties (428).

The comparison of blood flow through different parts of the lungs has generally involved either bronchspirometry or regional sampling of alveolar gas. Bronchspirometry has been particularly fruitful in comparing the perfusion of the two lungs; thus, simultaneous measurements of the uptake of each lung separately have disclosed that ordinarily each lung receives a share of the cardiac output which is proportional both to its gas volume (29) and to its ventilation (203). Accordingly, in man, the right lung receives 55 per cent of the cardiac output (135); this fraction is decreased when the subject turns on his side so that the left lung is down (29).

Bronchspirometric comparisons of oxygen uptake have also disclosed that gravity rearranges the distribution of the blood flow within each lung: as the human subject stands, the oxygen uptake of the lower lobes increases at the expense of the upper lobes, indicating a preferential distribution of blood flow to the lower lobes; the change in the pattern of the blood flow occurs even though the distribution of ventilation is little altered by the change in posture (286). It should be noted that the use of bronchspirometry to detect changes in regional blood flow presupposes that all parts of the lungs are breathing the same inspired mixture; when different parts of the lungs are given different inspired gas mixtures to breathe, the procedures and calculations grow much more complicated since all of the variables in the Fick equation—instead of only the oxygen uptake—have to be determined (135, 221, 410).

Hemodynamic measurements (247) and analyses of alveolar gas have been consistent with the bronchspirometric measurements. For example, the alveolar gas analyses have shown that: *a*) the oxygen tension of the upper lobes exceeds that of the lower lobes (285, 330); *b*) the carbon dioxide tension of the upper lobes is less than that of the lower lobes (284, 330, 388); and *c*) the respiratory exchange ratio of the upper lobes exceeds that of the lower lobes (428). All these observations are consistent with the clinical belief that high oxygen tension in the apices of the lungs, resulting from inadequate perfusion with respect to ventilation, is responsible for the apical localization of pulmonary tuberculosis (344). They also indicate that if intrapulmonary baroreceptor mechanisms for rearranging pulmonary blood flow do exist at the pulmonary bases, they are easily overwhelmed by the mechanical effects of gravity.

The combination of xenon¹³³ and external counting was originally used to estimate the distribution of inspired air (32, 234). Subsequently, oxygen¹⁵ (107) and then oxygen¹⁵-labeled carbon dioxide (427) were introduced to relate the distribution of the perfusion to the distribution of the inspired air. In addition to confirming that in the seated normal subject the lower lobes are much better perfused than the upper (8:1) (428), these studies also expressed, in quantitative terms, the spectrum of ventilation-perfusion ratios which exist in the lungs of upright normal man, and showed how the ratios gradually convert from high to low values as the base of the lung is approached. Moreover, although these inhomogeneities have inevitable consequences for the gas tensions in the regional alveoli and capillaries, they were shown to have little significance for the efficiency of the lung in oxygen uptake or carbon dioxide output. Finally, the intrapulmonary distribution of air and blood was demonstrated to become much more uniform when the normal subject assumed the supine position or when mechanical influences, such as anatomical restriction of the lower pulmonary vascular bed by congestion and fibrosis, counteracted the tendency of gravity to direct blood to the lower lobes in the upright position (107).

Because the normal lung is too inhomogeneous and too complicated to be treated in simple mathematical terms, conceptual models of alveolar-capillary gas exchange have been adopted as practical tools for assessing the adequacy of pulmonary capillary perfusion. One particularly useful model has been the homogeneous "ideal" lung, a figurative lung to which actual inhomogeneities can be referred (266,

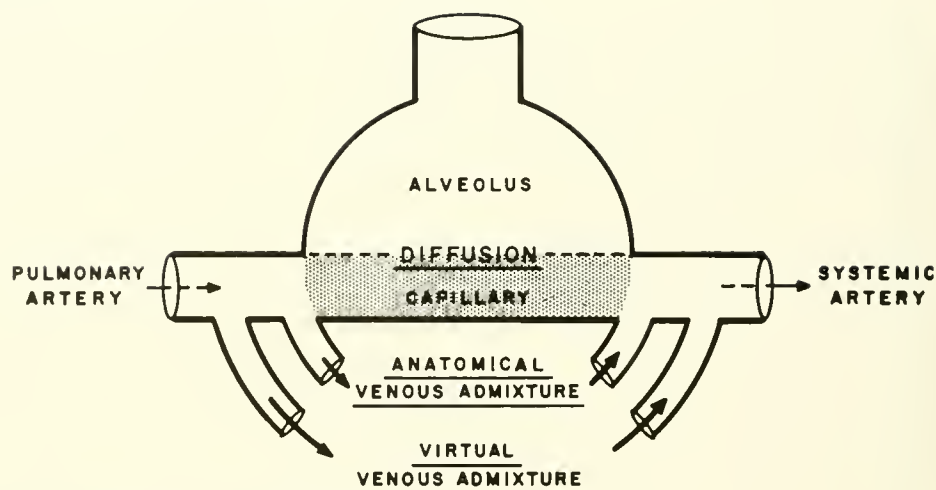


FIG. 14. Model of the lungs. Any inhomogeneity of ventilation and perfusion is represented as "virtual venous admixture." Pulmonary arteriovenous shunts appear as "anatomical venous admixture." According to this model, the alveolar-arterial difference in oxygen tension may be subdivided into three components: diffusion, virtual venous admixture, and anatomical venous admixture. As indicated in the text, this is an oversimplification. [After Briehl & Fishman (51).]

327, 345): the standard tactic is to express deviations from homogeneity in terms of their effect on the alveolar-arterial differences in oxygen tension ("A-a gradient"). By partitioning the A-a gradient into three components (fig. 14), it is possible not only to identify the venous admixture component, but also to separate it into anatomical and "virtual" portions; the "virtual" venous admixture is then an expression of the inhomogeneity of pulmonary capillary perfusion with respect to other gas-exchanging parameters (14, 23, 51).

The picture which has emerged from this type of approach is illustrated in figure 15: alveoli which are excessively perfused for their ventilation ($\dot{V}_A/\dot{Q} < 0.8$) contribute to the virtual venous admixture; those which are perfused but nonventilated ($\dot{V}_A/\dot{Q} = 0$) appear as anatomical venous admixture; those which are excessively ventilated for their perfusion ($\dot{V}_A/\dot{Q} > 0.8$) contribute to the "physiological" dead space, the "alveolar" dead space, and to the alveolar-arterial gradient for carbon dioxide (347, 377).

While this model is the basis of much of contemporary thinking about the distribution of blood flow with respect to gas exchange, it is known to be inadequate on several practical and theoretical accounts: *a*) the fractionation of A-a gradient is technically difficult and apt to be imprecise, especially in patients with diffuse pulmonary disease; *b*) the model does not recognize other inhomogeneities, e.g., between perfusion and diffusing capacity or between stroke output and pulmonary capillary blood volume, which

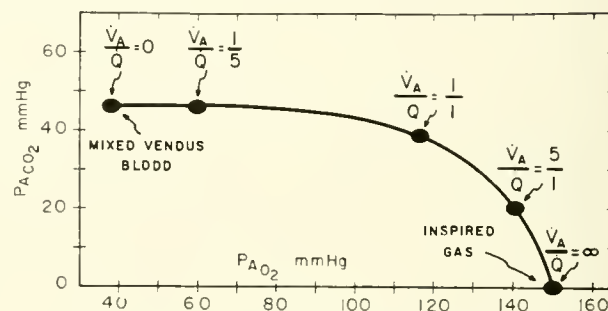


FIG. 15. Hypothetical distribution of alveolar ventilation-perfusion ratios (\dot{V}_A/\dot{Q}) within the normal human lung. Values for \dot{V}_A/\dot{Q} range from zero at the mixed venous blood point (perfusion but no ventilation) to infinity at the inspired air point (ventilation without perfusion). According to this model, the \dot{V}_A/\dot{Q} ratio of each alveolus fixes its respiratory exchange ratio (*R*) as well as its gas tensions ($P_{A_{N_2}}$, $P_{A_{O_2}}$, and $P_{A_{CO_2}}$). [Based on Riley & Cournand (345) and Rahn (327).]

consequently appear as imbalances between ventilation and perfusion (319, 413); and *c*) basic assumptions, such as the type of statistical distribution of ventilation-perfusion ratios among the alveoli may be erroneous (128).

In practice, the mixing formula shown in figure 16 is generally applied to data obtained during ambient air breathing to determine the total venous mixture, i.e., the sum of the anatomical and the virtual; by repeating the measurements during high-oxygen breathing, the virtual component is minimized so that the venous admixture consists almost entirely of the anatomical component (23).

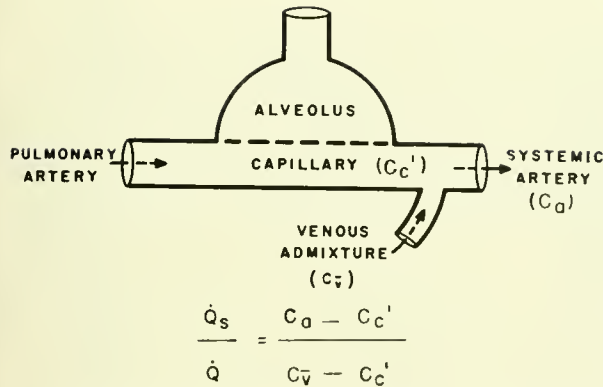


FIG. 16. Schematic representation of the lung to illustrate the components of the venous admixture and the calculation of the venous admixture as a fraction of the cardiac output. \dot{Q}_s = venous admixture (anatomical plus "virtual"); \dot{Q} = cardiac output; C_a , C_c , C_v = oxygen content of arterial, end-capillary, and mixed venous blood, respectively. Furthermore, by administering enriched-oxygen mixtures, the total venous admixture (\dot{Q}_s/\dot{Q}) can be subdivided into its anatomical and "virtual" portions.

Attempts have also been made to measure anatomical venous admixture in other ways, e.g., the simultaneous intravenous injection of T-1824 and Kr⁸⁵; unfortunately, such methods are most reliable when the anatomical venous admixture is large, i.e., greater than 15 per cent of the cardiac output (155).

In recent years, relationships between pulmonary capillary perfusion and other gas-exchanging parameters have been clarified in many different ways: *a*) the determination of alveolar-arterial gradients for nitrogen (67, 232); *b*) the quantification of the role played by parameters other than ventilation and perfusion in determining virtual venous admixture (319); *c*) the comparison of anatomical dead spaces with physiological and alveolar dead spaces (347, 377); *d*) the analysis of the pulmonary elimination of intravenously injected radioactive tracers (173); and *e*) by the creation of new and more elaborate models (52, 131). With the growth of understanding of these interplays has come the fuller appreciation of the extent to which they may affect conventional tests of pulmonary performance and calculations of pulmonary resistance.

PULMONARY VASCULAR PRESSURES

Recording

The characteristics of adequate manometric systems as well as the limitations of the cardiac catheter in

reproducing the intravascular and intracardiac pressure pulses are considered elsewhere in this volume. However, it should be emphasized that with modern, hi-fidelity recorders and manometers, it is generally the catheter attached to sensing element, rather than the manometric system, which limits the capacity of the apparatus to duplicate faithfully the pressure pulse. It is also noteworthy that even though blood pressure recorded from the end of a catheter in the pulmonary artery is sufficiently exact for most physiologic purposes, it fails to measure the lateral pressure in the vessel by a small, but variable, amount.

Hydrostatic Reference Level

For the measurement of absolute pressures within the thorax, correction is made for the hydrostatic pressure difference between the intrathoracic site from which pressure is being recorded and the externally-placed sensing element of the manometer (169). For this purpose, the plane of the sensing element is set in relationship to both the heart and to some thoracic landmark. In practice, different hydrostatic zero levels have been adopted: most popular are levels 5 cm below the angle of Louis (253) and 10 to 12 cm above the tabletop (103). While the different reference levels do complicate the comparison of data from different laboratories, each is a perfectly reliable standard for comparing consecutive measurements in a single animal.

Several uncertainties creep into the use of fixed external references to obtain absolute values of intrathoracic blood pressures, particularly in patients who are dyspneic from cardiac or pulmonary disease. Thus, in subjects with large hearts or unusual configurations of the chest, it may be difficult to estimate precisely the difference between the external reference plane and the intracardiac site of reference (253); moreover, even in normal subjects, the heart changes position during each cardiac cycle. Consequently, it seems reasonable to view pulmonary vascular and intracardiac pressures which are measured in this way as accurate only to within a few mm Hg.

Unfortunately, many intuitively attractive solutions to the problem of "zeroing" are not feasible: the tip of the cardiac catheter, as localized by X ray, cannot, per se, serve as the zero reference plane; nor is it a simple matter to "zero" an intracardiac manometer which is built into the tip of a cardiac catheter. Nonetheless, despite these difficulties inherent in the choice of reference levels for absolute

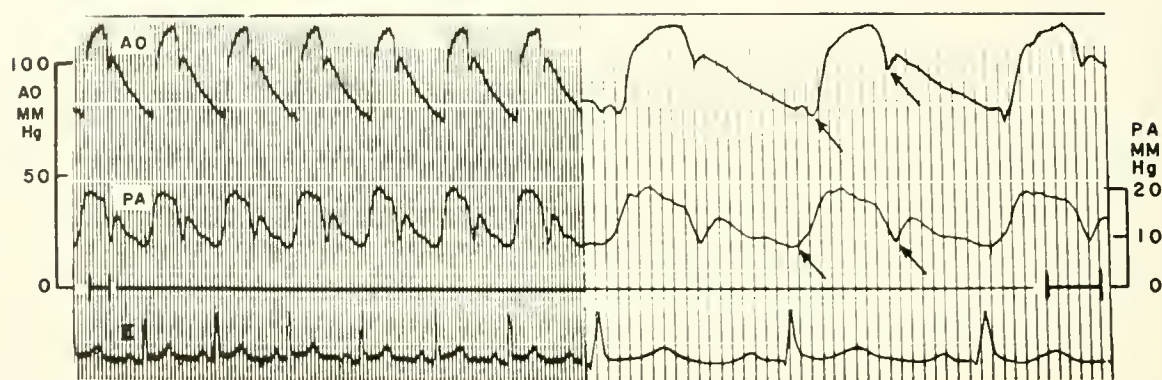


FIG. 17. Simultaneous aortic (AO) and pulmonary arterial (PA) pressure pulses recorded from a human subject with a normal circulation during open thoracotomy. The arrows indicate the beginning of ejection and the end of protodiastole in the aorta and pulmonary artery. (Paper speed, 25 mm/sec on left; 75 mm/sec on right. Interval between time lines, 0.04 sec.) [After Braunwald *et al.* (47).]

values, any of these reference levels will suffice for consecutive measurements in a single experiment.

Pulmonary Arterial Pressure

With minor differences, the contour of the pulmonary arterial pulse mirrors that at the root of the aorta: as may be seen in figure 17 (47), the pulmonary arterial pressure pulse is small in amplitude as compared to the aortic pulse and characteristically displays a rapid rise to a rounded peak during systole, a brisk small incisura and a gradual decrease in pressure during diastole (182, 225). The "classical" pulmonary arterial curves are more apt to be recorded in pulmonary hypertensive states than in pulmonary normotensive states; at the lower levels of pulmonary arterial pressure, distorting artifacts are exceedingly common. Not shown are the corresponding records of the velocity of the blood flow: in contrast to the pressure-velocity relationships in the aorta, the pulmonary arterial pressure-velocity curves are quite similar: the velocity of blood flow in the pulmonary artery lags slightly behind the pulmonary arterial pressure (156).

Ordinarily, the pulmonary arterial mean pressure in man (87), dog (303), cat (132), and the rabbit (239) averages one-fifth to one-sixth that in the systemic circulation. In man, the level of the pulmonary arterial pressure seems to increase slightly with age (101). There is no fixed relationship between the pressures in the two circuits. In man, before the onset of systole, the pulmonary arterial pressure is of the order of 7 to 12 mm Hg; during systole it rises abruptly to 20 to 30 mm Hg; the corresponding

mean pressure is of the order of 12 to 15 mm Hg (87, 103). In the dog, pulmonary arterial pressures tend to be somewhat higher, so that a mean pressure of 20 mm Hg is not unusual (187).

Pulmonary Venous and Left Atrial Pressures

Blood pressures have been recorded directly from the left atrium and pulmonary veins in dog (187) and man (45, 92, 299). The pulmonary venous pressure pulse is a record of left atrial events, indicating that the pulmonary arterial pressure pulse has been damped out by the small pulmonary vessels. As in the systemic veins and right atrium, the *a*, *c*, and *v* waves are clearly defined (187); but, in contrast to the right heart, the summit of the *v* wave is usually the highest part of the pressure pulse, and pressure variations during the cardiac cycle are greater in the left atrium and pulmonary veins. Thus, in both the unanesthetized and anesthetized dog, pulmonary venous pressures during a single cardiac cycle range between 3 and 12 mm Hg (187). In intact, unanesthetized man the mean left atrial pressure is of the order of 4 to 5 mm Hg (47). Although physiologic observations (121) are accumulating to support the anatomic impression (56, 392) that the pulmonary venous-left atrial junctions can act as sphincters, final proof, in the form of suitably recorded pulmonary venous-left atrial pressure gradients or differences between the contours of the pulmonary venous and left atrial pressure pulses have as yet not been published.

Until recently, measurements of left atrial and pulmonary venous pressures in intact animals were

confined to dogs fitted with angiostomy cannulae (150, 225); in recent years, these pressures have been measured in both intact animal and man by every conceivable route: right heart catheterization in patients with congenital atrial defects, direct cardiac puncture, transbronchial puncture, trans-thoracic puncture, and intracardiac transeptal puncture (45, 299).

Pulmonary Arteriovenous Pressure Gradient

In man, cat, and dog, the pressure drop across the pulmonary vascular bed is of the order of one-tenth of the pressure drop across the systemic circulation. The pulmonary arterial-left atrial pressure gradient is maximal early in systole (fig. 18); it decreases late in systole and may even approach zero if diastole is sufficiently prolonged (182). Unfortunately, since both the pulmonary arterial and pulmonary venous pressure pulses have different origins (right and left sides of the heart, respectively), it is not possible to predict the shape of the pressure pulses of the intervening vascular bed from the pulmonary arterial-pulmonary venous pressure gradient.

Pulmonary Wedge Pressures

The pulmonary arterial wedge pressure is recorded by advancing a cardiac catheter until its tip occludes a terminal branch of the pulmonary artery; flow then

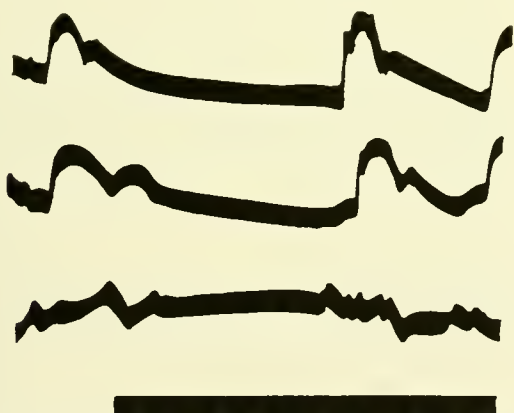


FIG. 18. The pulmonary vascular pressure gradient. *Upper curve*: record of the pulmonary arterial pressure pulse of an unanesthetized, unoperated dog; blood pressure 35/12 mm Hg, mean 20 mm Hg. *Lower curve*: record of the pulmonary venous pressure pulse; blood pressure 2 to 12 mm Hg. *Middle curve*: differential manometer record of pulmonary arterial minus pulmonary venous pressure, i.e., the gradient of pressure driving blood through the pulmonary vascular system. [After Hamilton (182).]

stops in the vascular segment beyond the tip of the catheter: the pressure transmitted by the intervening static column of blood presumably approximates closely the pressure in the first communicating pulmonary veins in which flow persists. Pulmonary venous wedge pressure is recorded by impacting a catheter (passed retrograde) in a pulmonary vein.

Originally (200), it was believed that the wedged pulmonary arterial pressure could be used as a measure of pressure in the pulmonary capillary bed. It is now clear that the wedged arterial catheter registers more remote events, i.e., events in the large pulmonary veins and, unless the "throttles" actually operate, in the left atrium (83). In both dog and man—with normal pulmonary circulation or with pulmonary venous congestion—the mean pulmonary arterial wedge pressure and the mean left atrial pressure are nearly identical (83). In the normal animal and man, the level of the arterial wedge pressure is of the order of 5 to 9 mm Hg (103); in patients with pulmonary venous congestion from mitral stenosis, it parallels the left atrial and pulmonary venous pressure.

The validity and meaning of the arterial wedge pressure have been the subjects of considerable debate (26). Various criteria have been adopted for deciding if a wedge pressure is a reliable measure of the level of the left atrial pressure; these include higher pulmonary arterial mean and diastolic pressures than the recorded wedge pressure, the withdrawal of fully oxygenated blood from the impacted catheter, the snap of the catheter as it is withdrawn from the wedge position and a characteristic configuration of the wedge tracing (83, 103). No single one of these criteria ensures a reliable measure of left atrial pressure, particularly when pressure is changing rapidly (26). Indeed, even when all criteria are met, the left atrial pressure may be poorly transmitted due to a faulty wedge position of the catheter (fig. 19) (22).

The use of the arterial wedge pressure as a measure of the level of left atrial pressure is on sounder footing than its use to record the contour of the left atrial pressure pulse. Only in states of pulmonary venous congestion is the wedge catheter apt to reproduce cyclic events in the left atrium (83, 113). Interpretation of changes in contour is particularly troublesome when artifacts are present; these artifacts tend to be most pronounced during exercise and deep breathing.

Blood pressure falls in the pulmonary artery distal to an occlusive balloon and assumes the nondescript character of a wedge pressure (fig. 20) (49, 42). The level of this distal pulmonary arterial pressure corresponds to that in the left atrium and fluctuates

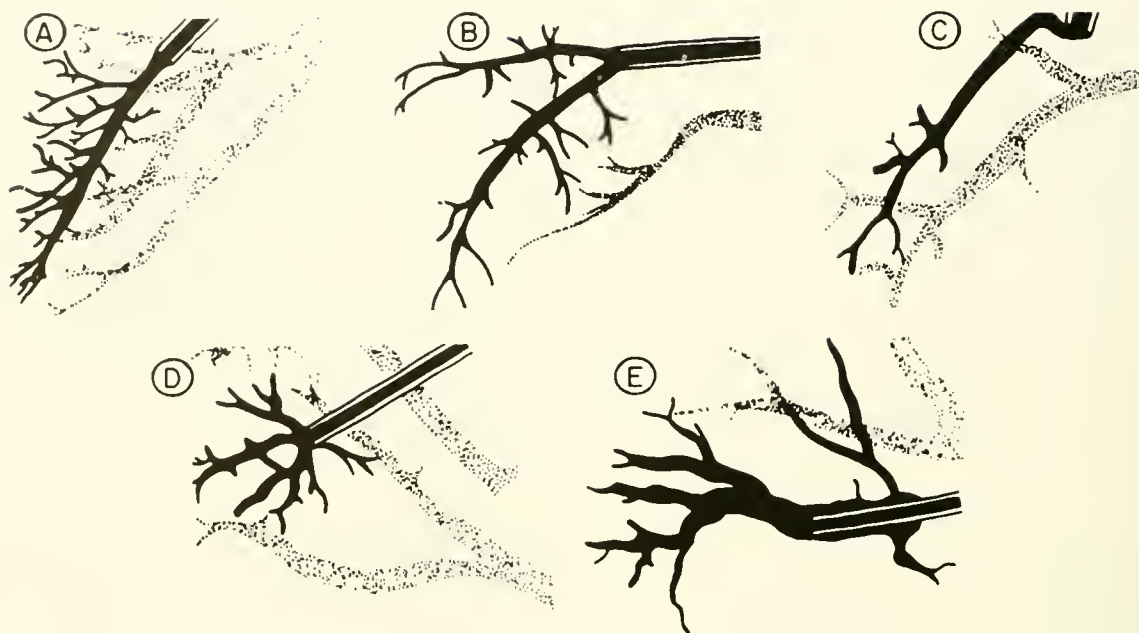


FIG. 19. Various positions of the "wedged" catheter redrawn from pulmonary wedge arteriograms. *A*: the catheter is wedged in an artery which is slightly smaller than the catheter tip; the lumen of the artery is in direct line with the lumen of the catheter. *B*: the catheter is wedged at a bifurcation of an artery of the same size as the catheter tip. *C*: the tip of the catheter impinges against the wall of a sharply angulated artery. *D*: The catheter is wedged at a point where the artery divides into three or more branches. *E*: the catheter is incompletely wedged. The injected dye regurgitates around the catheter outlining the artery proximal to the catheter tip. Positions *A*, *B*, and *D* are favorable for recording wedge pressure; positions *C* and *E* are not. [After Bell *et al.* (22).]

with changes in the left atrial pressure. The tracing shows no left atrial or pulmonary venous events but does display respiratory swings.

Pulmonary venous wedge pressures have also been recorded in the dog (435), in normal human subjects (84, 248), and in patients with atrial septal defects. In the normal dog the pulmonary venous wedge pressure approximates mean pressure in the pulmonary artery (435); in patients, with pulmonary hypertension, the pulmonary arterial mean pressure is much higher than the pulmonary venous wedge pressure, presumably due to the interposed high vascular resistance (84).

In brief, neither the pulmonary arterial wedge pressure nor the pulmonary venous wedge pressure provides a measure of the pulmonary capillary pressure. However, with care and under appropriate circumstances, the pulmonary arterial wedge pressure does provide an approximate measure of the pulmonary venous, and usually, of the mean left atrial pressure; it can then be used to estimate the driving pressure across the entire pulmonary vascular bed and to calculate the resistance to perfusion offered by the small pulmonary vessels.

Influence of Intrathoracic Pressure on Pulmonary Vascular Pressure

Pressure in an intrathoracic vessel is not a simple concept. In order for such a pressure to have meaning, it must be related to a reference level, i.e., atmospheric or pleural pressure. If the manometer which records the pressure is balanced against atmospheric pressure, all pressure changes within the thorax arising from the ventilation—for example, a cough (fig. 21)—will be immediately propagated across the walls of the pulmonary vessels and heart to the incompressible blood which they contain; the intrathoracic pressure changes will, therefore, be registered as an integral part of the pressure pulse. However, pressures recorded in this way ("luminal" pressures) provide no measure of the pressure which distends the vessels ("transmural" pressures): during a cough, while the pressure recorded by a manometer balanced against atmospheric pressure rises precipitously, a manometer balanced against pleural pressure shows that the transmural pressure has remained virtually unchanged (190).

Values for the pleural pressures have been obtained

in various ways, including direct measurements from gas pockets and balloons within the pleural or mediastinal spaces (82) and indirect estimates from the esophagus (287). It is generally conceded that

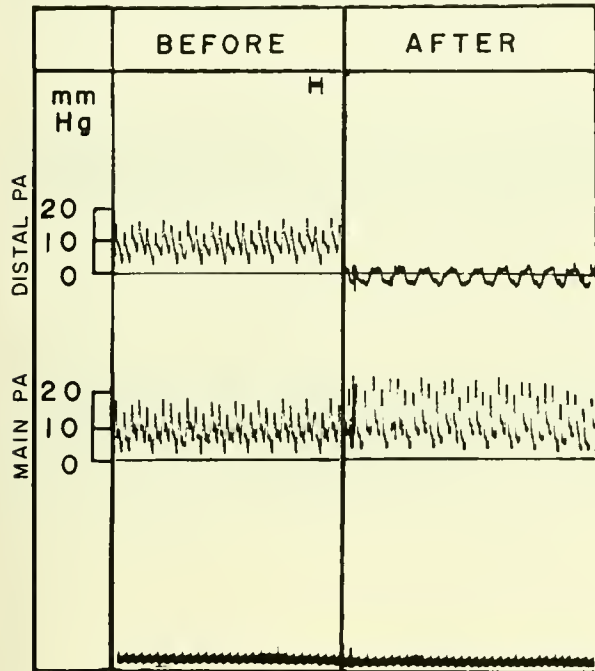


FIG. 20. Effect of occluding the right pulmonary artery on blood pressures distal and proximal to the occlusive balloon. Before occlusion, blood pressures are identical in the main and right pulmonary arteries. After occlusion, the distal pressure falls to the level of pulmonary wedge pressures (left atrial pressure); pressure in the main pulmonary artery proximal to the balloon increases by approximately 5 mm Hg. (Unpublished observations of M. Brandfonbrenner, A. Himmelstein, G. M. Turino, and A. P. Fishman.)

even the direct methods may fail to provide precise measurements of the pressures which are operating at the surface of the particular pulmonary vessels under consideration: the pressure within the pleura may not be entirely uniform (82, 127); the extramural pressures along the length of the vascular tree may differ from segment to segment and from the pleural pressure, depending on the location of the segment, i.e., intrapericardial, intrapulmonary, or juxta-alveolar. The use of indirect measures, which provides reliable measures of pleural pressures in some experimental and clinical conditions, fails in others (287).

Transmural Versus Luminal Pressures

During each respiratory cycle, the changing pleural pressures (fig. 22) affect all intrathoracic vessels except those apposed to alveoli. Consequently, for the alveolar capillaries, the pressure which determines their caliber, i.e., transmural pressure, is customarily calculated as the difference between (estimated) intracapillary and alveolar pressure; the transmural pressure of all other vessels is calculated as the difference between the luminal and the pleural pressure (fig. 23) (61, 233). The practical difficulties in estimating perivascular pressure from pleural pressure have been indicated above; pericapillary pressures also have an element of uncertainty because of the prospect that tissue forces, such as alveolar surface tension, may decrease pericapillary pressure to sub-atmospheric levels.

Depending on the purpose of the observation, pulmonary vascular pressures are referred either to atmospheric or to pleural pressure. Considerable

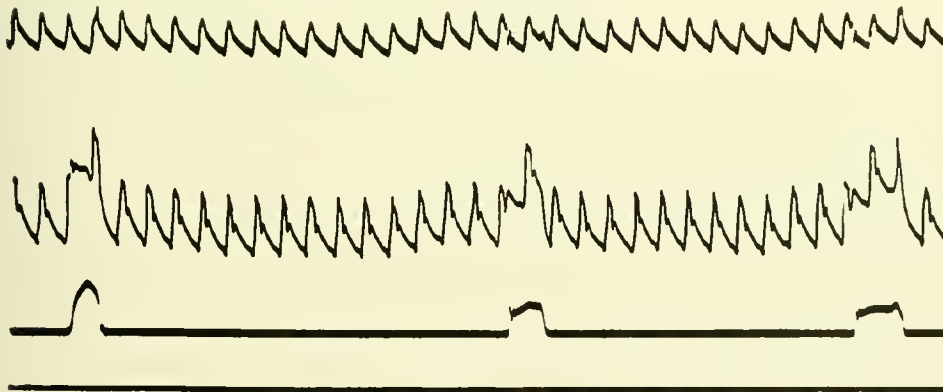


FIG. 21. Differential pressure record of a "cough." The lowest tracing is from a mouthpiece into which a forcible expiration was made. The middle record is that of luminal systemic arterial pressure. The upper record is a differential record of the middle minus the lower record. The mouthpiece record is assumed to show pressure changes nearly identical with intrathoracic pressure changes; the differential record indicates the stresses which the intrathoracic arteries undergo. [After Hamilton *et al.* (190).]

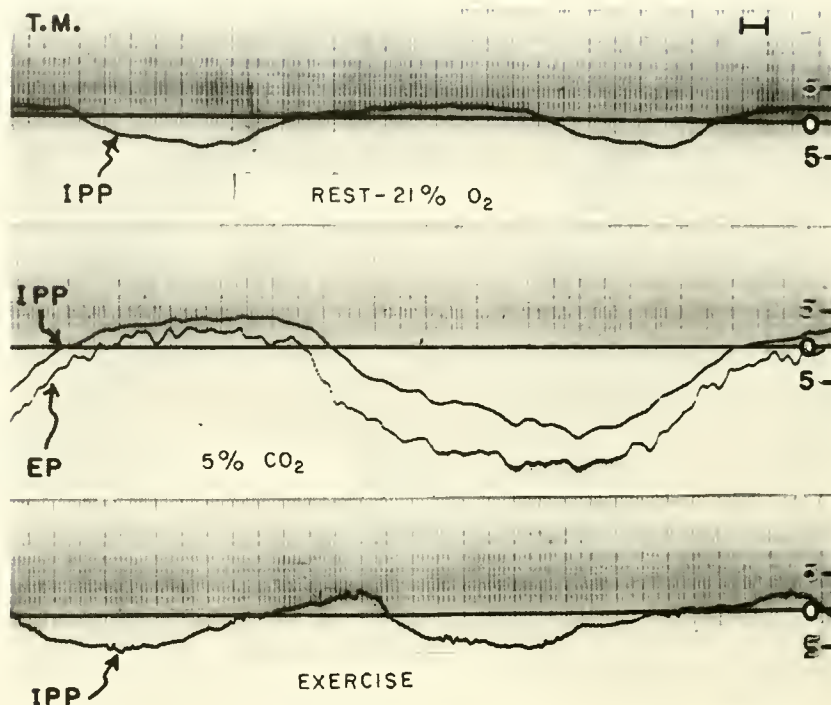


FIG. 22. Effects of breathing 5% CO_2 and of exercise on the pleural pressures (IPP) and esophageal pressures (EP) of a human subject. All pressures are in mm Hg. [After Fishman *et al.* (132).]

confusion has arisen from the indiscriminate use of transmural pressures for luminal pressures in the calculation of pulmonary vascular resistance. It should be emphasized that as long as left atrial pressure exceeds alveolar pressure, the measurement of the driving pressure across the lung requires only the simultaneous measurements of luminal pulmonary arterial and venous pressures—no matter what the intrathoracic pressure may be.

PULMONARY BLOOD VOLUME

The pulmonary vasculature constitutes a distensible reservoir, interposed between the right and left heart. The volume of blood which it contains is of interest on three separate accounts: 1) the mechanical behavior of the lungs; 2) the efficiency of gas exchange; and 3) the sustained return of pulmonary venous blood to the left heart. In large part, the volume of blood contained in the lungs at any instant is determined passively by the balance between pulmonary inflow, i.e., between the output of the two ventricles; it is also influenced considerably by the ventilation. Whether an element of self-control is also provided by pulmonary vasomotor activity, particularly on the part of the veins (305) or of hypothetical venous sinuses (381), is uncertain.

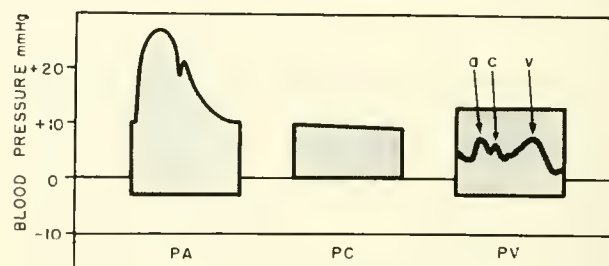


FIG. 23. Difference between luminal pressures (referred to atmosphere) and transmural pressures (referred to perivascular pressure) along the length of the pulmonary vascular tree. The shaded area represents the luminal pressure. In the capillaries (PC), which are exposed to alveolar pressure, the luminal and transmural pressures are virtually identical. On the other hand, in the pulmonary artery (PA) and vein (PV), the transmural pressure exceeds the luminal pressure by the pleural (perivascular) pressure.

Measurement of Pulmonary Blood Volume

For convenience, the methods for measuring pulmonary blood volume may be sorted according to whether they are designed to measure the pulmonary blood volume or a change in pulmonary blood volume.

In the isolated lung or in thoracotomized animals, the pulmonary blood volume is available for direct mensuration (293, 384); but, because of the surgical manipulations and the drastic experimental conditions, the measured volume may differ considerably

from the volume which prevails under more natural conditions. In intact animal or man, indicator-dilution techniques have been commonly used to approximate the size of the pulmonary blood volume.

STEWART-HAMILTON: INDICATOR DILUTION. This is an indicator-dilution method (fig. 24) which entails the introduction of a test substance into the venous side of the circulation and the registration, from a systemic artery, of its changing concentration with time (18, 111, 184). This application was first proposed by Stewart (184), who held that the product of the flow and the appearance time of the injected substance is a measure of the capacity of the bed through which the flow takes place; this idea was shared by Blumgart and Weiss (184). Hamilton and collaborators (186) showed that the mean circulation time rather than the shortest circulation time should be used to calculate the volume of blood in the vascular bed between the point of injection and the point of sampling. In a simple model, in which the entire stream passes the points of injection and of sampling, the idea that the product of the flow and the mean circulation time measures the intervening volume is not only acceptable intuitively, but has also been checked in models (186) and proved mathematically (444). Since the mean circulation time is approximately the time ordinate corresponding to the center of gravity of the time-concentration curve (fig. 25A), the substitution of the median for the mean circulation time may introduce considerable error into the calculation (184).

The injection into the venous circulation coupled

with sampling from a peripheral artery defines only a "central blood volume"; its limits are wide and vague: it includes not merely the blood volume between the needles, but also the volume of blood contained in the other branches of the venous and arterial trees having equivalent circulation times. It is a virtual volume which corresponds to an anatomical volume only under ideal conditions: if mixing of blood and tracer is complete and uniform, if the system contains neither stagnant nor sequestered blood and if there are no preferential channels which are operating to short-circuit the system. The use of mathematics to construct a continuous infusion curve from the single injection curve involves identical premises and does not make the measurement of the pulmonary blood volume any more definitive. The continuous infusion of a tracer substance into the central circulation does provide an alternate approach for measuring the pulmonary blood flow and central blood volume (fig. 25B) (444); however, as in the case of the single injection, the results promise to be less precise for volume than for flow (444).

When the test substance is injected into a peripheral vein (instead of into the pulmonary artery), the central blood volume includes the whole cardiac blood volume. Many different radiological techniques have been applied to the measurement of the cardiac blood volume in dog and man (151). Despite theoretical reservations of various kinds—such as the difficulty in separating the contribution of cardiac cavities and walls to the radiographic picture of the heart—the radiographic cardiac volume in dogs was found to correspond, within 10 per cent, to the directly meas-

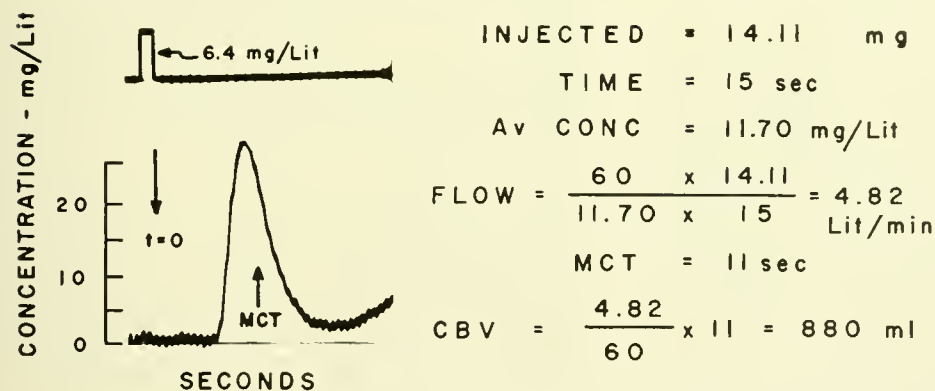


FIG. 24. Concentration-time curve inscribed by densitometer through which peripheral arterial blood was drawn at a constant rate following injection of T-1824 into the pulmonary artery of a normal human subject. At $t = 0$, the indicator was injected. The calibration marks at the top of the record indicate that a deflection of 1 cm is equal to a concentration of 6.4 mg of dye per liter of blood. From such a record, the pulmonary blood flow, the mean circulation time (MCT), and the central blood volume can be calculated as shown.

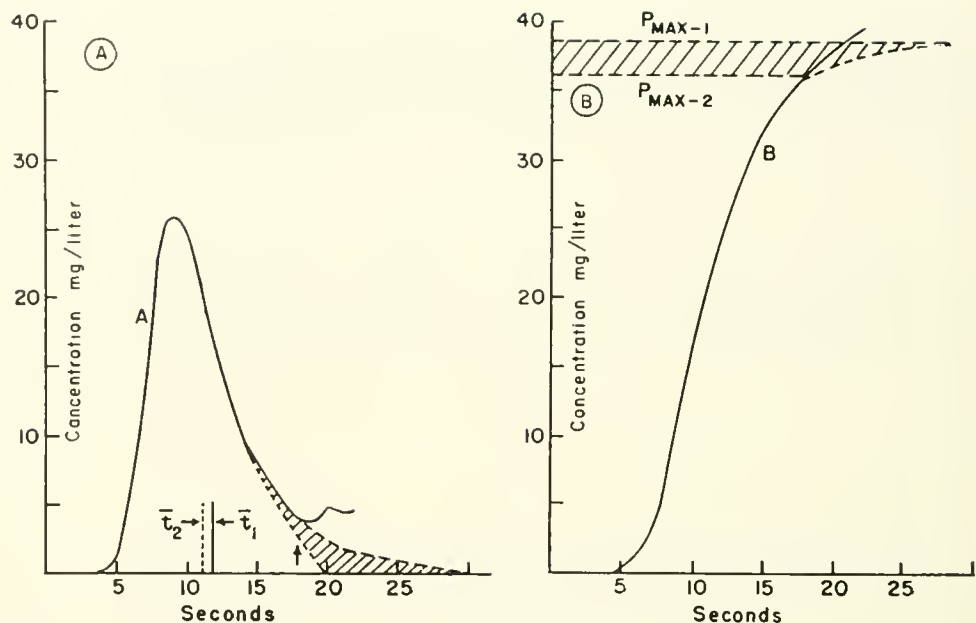


FIG. 25. Schematic representations of concentration-time curves following injection of indicator into central circulation. *A*: single injection curve. Recirculation of indicator occurs at arrow. The dashed lines illustrate likely extremes of extrapolation of the downlimb to zero during the first circulation of indicator. The shaded arrow represents the relative difference between the two estimates of blood flow based on the two extrapolations. The vertical lines \bar{t}_1 and \bar{t}_2 represent the two estimates of mean transit time based on the two extrapolations. If recirculation occurs earlier, so that the shape of the downlimb is uncertain, considerable errors may be introduced by the extrapolation. *B*: constant injection curve. The times at which the indicator just appears and recirculates are identical with those in panel *A*. The dashed lines represent likely extrapolations to a plateau concentration. The shaded area between P_{MAX-1} and P_{MAX-2} represents the difference between estimates of area above the extrapolated buildup concentration curves. The problem of recognizing the point of recirculation is the same as for the single injection curve of panel *A*. [After Zierler (444).]

ured volumes (184); moreover, following epinephrine overdosage, the radiographic cardiac volume was found to constitute an unusually large fraction of the central blood volume (151, 184). By substituting cineradiography of the opacified intracardiac volumes for conventional radiography, the precision of the radiographic approach has been greatly enhanced (73, 170, 367); this modification promises a reliable measure of the volumes of the individual chambers in normal man and dog. It remains to be seen if precise measurements of this type can also be made in patients with pulmonary congestion and cardiomegaly.

Recently, the central blood volume has been experimentally narrowed to the pulmonary blood volume by the use of two catheters—one in the pulmonary artery and the other in the left atrium. Once placed, the catheters have been put to different uses: *a*) for injecting a tracer substance into the pulmonary artery and for sampling from the left atrium (246, 293), and *b*) for injecting tracer substances into both the pulmonary artery and left atrium, and

sampling from the brachial artery, thereby determining the mean pulmonary arterial-left atrial transit time (106, 278). Although the second of these approaches was designed to circumvent the theoretical possibility of incomplete mixing in the left atrium, the values for the pulmonary blood volume by both approaches have been not only similar, but also surprisingly low.

NEWMAN: EXPONENTIAL DOWNSLOPE. The time-concentration curve of injected substance typically has a descending exponential limb. According to Newman (304), the slope of this line measures the volume of a model through which water is perfused if there is instantaneous and complete mixing of injected dye and perfusate. If several chambers are perfused in series, the slope indicates the volume of the largest. Assuming that the lung volume is the largest of those concerned in the circulation, Newman used the slope to obtain a measure of the pulmonary blood volume. In 1932, Hamilton *et al.* (186) had evolved an equa-

tion similar to that of Newman, but rejected the idea that the volume term in that equation could stand for a significant physiological volume because, in the physiological circuit, there is neither instantaneous nor complete mixing of dye with all of the blood in either heart or lungs. It now seems that the 1932 view is correct (111, 283, 417).

BRADLEY: EQUILIBRATION CURVES. The method originally devised by Bradley *et al.* for the estimation of splanchnic blood volume (41) has been applied by others to the estimation of the pulmonary blood volume (326). The method entails the determination of the amount of tracer substance contained in the system at equilibrium (cardiac output \times arteriovenous difference \times equilibration time) divided by the equilibration concentration of tracer. From the point of view of application to the lungs, the most vulnerable part of the equation is the arteriovenous difference. Experiments with models have shown that, in contrast to the splanchnic circulation, the pulmonary circulation is not suited for this type of equilibration method (46). Consequently, it is difficult to place much confidence in the measurements in man which find that all three methods—the Stewart-Hamilton, Bradley, and Newman—provide comparable values for the pulmonary blood volume (326), particularly when there are other theoretical and practical reasons to expect discrepancies (111).

Changes in Pulmonary Blood Volume

Many different approaches have been used to detect a change in pulmonary blood volume. They include: a) lung volumes, b) mechanics of breathing, c) radioactive tracers, d) teeter board.

LUNG VOLUMES. In normal subjects the vital capacity is less in the supine than in the upright position. Although part of this decrease may reflect a change in the position and tone of the diaphragm (296, 388), an increase in the pulmonary blood volume also seems to be involved since measures which interfere with systemic venous return to the lungs minimize, or prevent, the decrease in vital capacity (188). Clinically, a low vital capacity is found in pulmonary congestion (406). However, in such patients, particularly if pulmonary venous hypertension has been prolonged and severe, the lung volumes may be more encroached upon by pulmonary edema and fibrosis than by an expanded pulmonary blood volume (238, 378).

MECHANICS OF BREATHING. Pathologists have long been aware that the chronically congested lung is a stiff lung (415). In 1934, Christie and Meakins showed by measurements of pleural pressure in vivo that the chronically congested lung requires a greater distending force than the normal lung (287). Since then, more elaborate ways of measuring and expressing pulmonary distensibility, such as "compliance" (change in lung volume per unit change in pleural pressure) have come into general use for the study of both acute and chronic pulmonary congestion; for the sake of safety and expediency, and at some sacrifice of accuracy, esophageal pressures have been substituted for pleural pressures (fig. 26) (287).

The effects of acute pulmonary engorgement on pulmonary distensibility have been examined in animals (35, 146) and in man (33, 406). Such studies have shown that pulmonary venous hypertension has a considerably greater effect in reducing pulmonary compliance than does either pulmonary arterial hypertension or an increase in pulmonary blood flow (35); moreover, a decrease in vital capacity parallels a decrease in pulmonary compliance (406). But these studies have also clarified some of the uncertainties which attend the use of a change in compliance as a

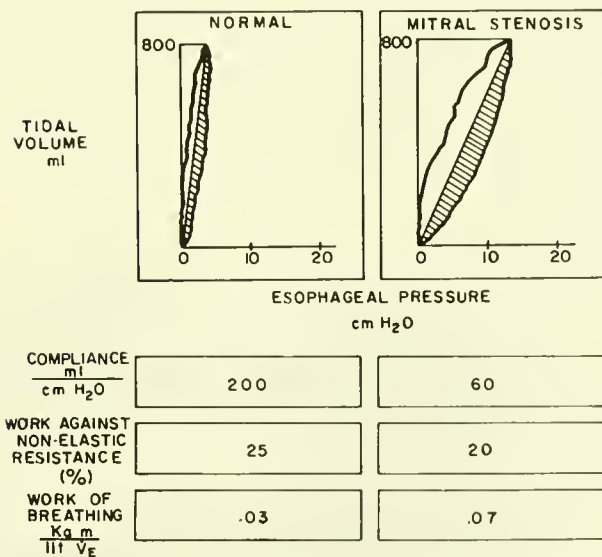


FIG. 26. Comparison of the pulmonary pressure-volume diagram of a normal subject with that of a patient with severe pulmonary congestion due to mitral stenosis. In the congested lung, the compliance ($\Delta V/\Delta P$) is approximately a third of normal and the resistance to air flow is normal. If pulmonary congestion is accompanied by edema of the airways ("cardiac asthma"), both the increased resistance to air flow and the stiffer lungs contribute to the inordinate work of breathing. [After Turino & Fishman (406).]

qualitative measure of the state of the pulmonary blood volume: an increase in pulmonary interstitial fluid during acute pulmonary venous hypertension may be indistinguishable from associated increase in pulmonary blood volume (378); the discrepancies between esophageal pressure and pleural pressure are exaggerated in the supine position since mediastinal contents compress the esophagus to yield artificially high values for pleural pressures; changes in the lung volume may, per se, affect apparent pulmonary distensibility (287).

Despite the limitations of methodology and the uncertain distinction between an expanded pulmonary blood volume on the one hand and its consequences on the other, pulmonary mechanics in pulmonary congestion continues to attract attention on several physiological accounts. For example, mechanical work and energy cost of moving congested lungs has proved to be abnormally high; moreover, in some obscure way, stiff lungs seem to set the characteristic breathing pattern (rapid frequency, small tidal volume) of pulmonary congestion (177, 406).

RADIOACTIVE TRACERS. Change in the radioactivity of a portion of the lung field after the intravenous administration of a radioactive tracer has been used as a measure of the change in pulmonary blood volume under various experimental conditions (271, 425). The validity of this approach rests heavily on the assumption that the external detector continues to survey an unchanged geometry throughout the

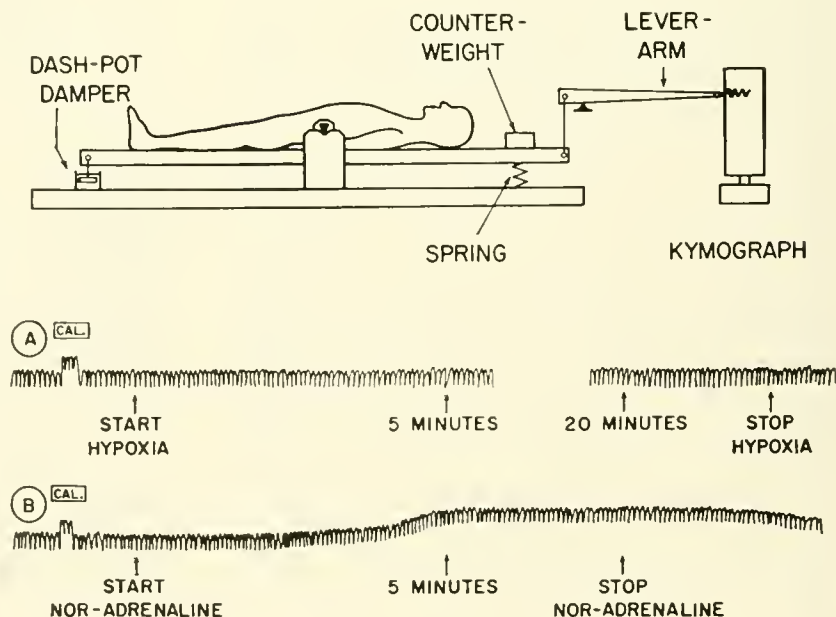
control and test periods. It is difficult to prove that this assumption is fulfilled in experiments which involve either respiratory maneuvers or changes in body position (425).

MISCELLANEOUS. Some experiments require only the recognition of a change in thoracic (instead of pulmonary) blood volume. For such experiments, the critically balanced teeter board has served as a useful device to detect a shift in the center of gravity of the body as blood is displaced from one end of the body to the other (fig. 27) (86, 154, 395). Also, the "cardiopneumogram" has provided an approach to the changes in thoracic blood volume during each cardiac cycle (185).

Normal Values for Pulmonary Blood Volume

It is meaningless to use the central blood volume—with its vague boundaries and its potential for internal rearrangement—as a measure of the pulmonary blood volume as long as the test substance is injected into a peripheral vein (184, 307). The first step to narrow the boundaries of the central blood volume was the pulmonary arterial injection of the test substance (coupled with peripheral arterial sampling); under these conditions, the central blood volume approximates 20 to 25 per cent of the total circulating blood volume (224, 249, 250). The second step was to couple the pulmonary arterial injection either with sampling from the left atrium or with the injection of a second

FIG. 27. The teeter board for detecting shifts in regional blood volumes. The records show that during acute hypoxia (A) the position of the center of gravity of the body remains unchanged; on the other hand, during the infusion of noradrenaline (B), the center of gravity shifts cephalad. CAL = calibration by placing a 200-gram weight at the angle of Louis. [After Fritts *et al.* (154).]



tracer into the left atrium. By these techniques, the pulmonary blood volume is of the order of 10 per cent of the total circulating blood volume (106, 246, 293).

It is surprising how closely the latter indicator-dilution value of 10 per cent in intact man corresponds to the more direct measurements in animals, i.e., dog, rabbit, and rat (293). The indicator-dilution value of 10 per cent also coincides with estimates based on pulmonary vascular dimensions in the dog (169).

Variations in Pulmonary Blood Volume

The pulmonary blood volume increases under a heterogeneous group of conditions (fig. 28): *a*) an increase in pulmonary blood flow (224, 250); *b*) inflation of an antigavity suit (33); *c*) negative (pleural) pressure breathing (397); *d*) the assumption of the supine position (381); *e*) systemic vasoconstriction from a variety of causes (64, 154, 186, 372); *f*) immersion in water (188); *g*) clamping of the pulmonary veins (114); and *h*) left ventricular failure and mitral stenosis (238).

Conversely, a decrease in pulmonary blood volume occurs during venesection and reduced cardiac output (184), positive pressure breathing and the Valsalva maneuver (44), systemic vasodilatation from warming (369, 381) and the assumption of the upright posture (247, 381).

Partition of Pulmonary Blood Volume

One particularly hazy aspect of the pulmonary circulation is the pattern in which the pulmonary

arteries, capillaries, and veins share the pulmonary blood volume under natural conditions, and the way in which this pattern is modified either by physiological stimuli or by disease. A few beginnings have been made: anatomical measurements in the dog suggest that the capacity of the pre- and postcapillary pulmonary vascular segments is approximately the same (169); observations on the isolated lung, while failing to define precise anatomical boundaries, have succeeded in disclosing how the pulmonary blood volume may be reapportioned in response to mechanical influences (124, 315, 317, 324) and to special stimuli (116, 305). However, there is no obvious way to apply these experimental observations to the arrangement of the pulmonary blood volume in life.

HEMODYNAMIC INTERRELATIONS

Distensibility and Resistance

In previous sections, pulmonary blood flow, volume and pressures were considered separately. The analysis of their interplay is a much more complicated matter. Generally speaking, the aim of such an analysis is to relate the static and dynamic properties of the pulmonary vascular tree to its architecture and to the structure of its walls. Until recently, investigators were preoccupied with the model of the pulmonary circulation which pictured it as the hemodynamic analog of an electrical d-c circuit and which viewed the pulmonary blood flow as though it were continuous and steady (169); for testing this conceptual model, the isolated lung seemed ideal on the

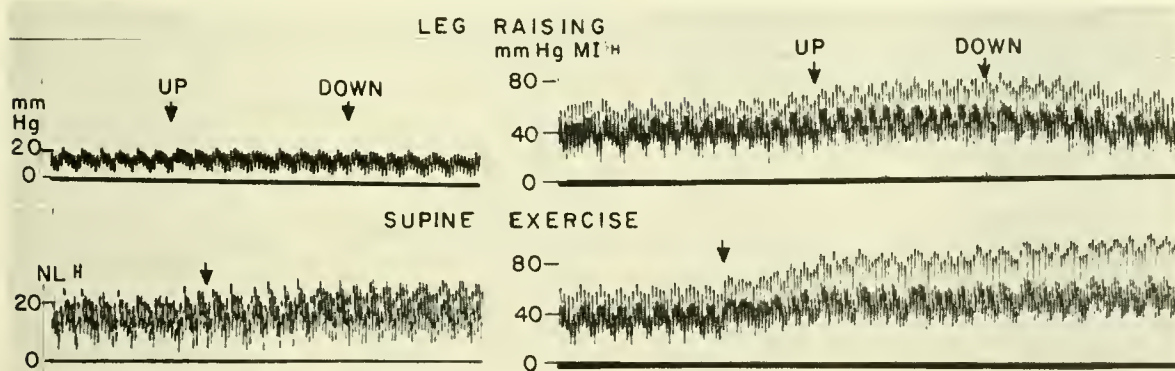


FIG. 28. Effects of leg raising and supine exercise on pulmonary arterial blood pressure. *Leg raising.* In the normal subject (*upper left*), leg raising is without appreciable effect on the pulmonary arterial pressure; in the patient with tight mitral stenosis (*upper right*), leg raising elicits a considerable increase in pressure. *Supine exercise.* In normal subject (*lower left*), exercise increases pulmonary arterial pressure by a few mm Hg; in the patient with tight mitral stenosis (*lower right*), the increase in pressure is much more striking. [After Turino & Fishman (406).]

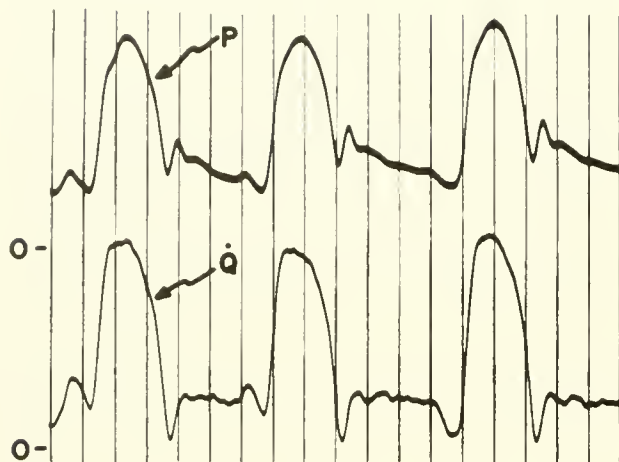


FIG. 29. Continuous records of pulmonary arterial pressure (P) and flow (\dot{Q}) from a closed-chest, unanesthetized dog. Blood pressure was recorded through a polyvinyl tube (encased in nylon) inserted through the wall of the main pulmonary artery about 1 cm distal to pulmonic valve. Blood flow was recorded by an electromagnetic flow meter (modified Kolin type) placed proximal to the bifurcation of the main pulmonary artery. Tubing and wires placed surgically and led to outside between scapulae. For calibration of flow meter, snares around right and left pulmonary arteries were tightened to arrest pulmonary arterial flow. (Courtesy of L. Fisher and D. E. Gregg.)

assumption that it simulated the geometry and distensibility of the pulmonary circulation in vivo. Within the last few years, investigators have begun to take a more realistic view of the pulmonary circulation, recognizing that hemodynamic events within it vary from instant to instant and that phasic differences between pressure and flow (fig. 29) are important; in order to treat these phasic events, they have resorted to a model based on electrical a-c theory (71, 177, 438). However, for the moment, this approach is handicapped by the technical difficulties of recording pulsatile pulmonary blood flow, especially in living systems (153, 237).

Distensibility and Capacity: Pressure-Volume Relationships

Because of the manner in which the pulmonary circulation is incorporated into the lung, the term "pulmonary vascular distensibility" is a composite one: it connotes not only the elastic properties of the vascular walls but also the tone of their smooth muscle, the perivascular air pressures, the effects of hidden forces such as alveolar surface tension (78, 312), the presence of excessive interstitial fluid (239), and the mechanical distortions of adjacent pulmonary

tissues (146). As in the systemic circulation, the distensibility characteristics are customarily expressed as the change in vascular volume per unit change in transmural pressure. However, in contrast to the systemic circulation, the small precapillary vessels are thin-walled and easily distensible, thereby contributing to the pressure-volume characteristics of the pulmonary arterial tree (350). This participation of the pulmonary "resistance" vessels in the "capacitance" function of the pulmonary circulation is of hemodynamic significance: for example, without pulmonary arteriolar sphincters, a larger fraction of the right ventricular stroke volume is apt to escape from the pulmonary arterial tree during and just after each systole than from the systemic arterial tree (240); also, during bradycardia the pulmonary arterial pressure may fall to the level of pulmonary venous pressures (187).

The distensibility characteristics of the pulmonary circulation, and of its individual segments, have been determined under a wide variety of experimental conditions, using greatly different types of preparations. These studies have led to certain generalizations: *a*) the pressure-volume characteristics of the entire vascular tree (fig. 30) and of the large pulmonary vessels resemble those of a large systemic vein (148, 211, 251, 290); *b*) as in other distensible structures, the blood pressure at any volume is higher when the system is being filled than when it is being emptied ("hysteresis," "delayed compliance," "stress-

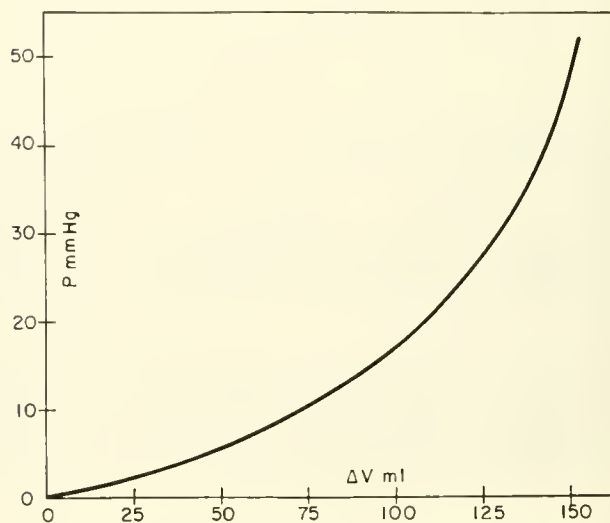


FIG. 30. Pressure-volume relationship of the pulmonary vascular bed in the dog. To construct this curve, blood was withdrawn at 10-sec intervals after initially elevating pressure in the system to approximately 60 mm Hg. [After Sarnoff & Berglund (371).]

relaxation") (318, 337, 371); *c*) the pulmonary venous-left atrial segment is less distensible than the systemic venous-right atrial segment (87, 272, 309); *d*) the successive segments of the pulmonary vascular tree differ considerably in distensibility [the veins and arteries are more distensible than the capillaries (124, 318)]; and *e*) although the aorta and pulmonary artery are of approximately the same caliber in life, the range of maximum distensibility for the pulmonary artery (10 to 40 mm Hg) is much lower than for the aorta (182). Unfortunately, measurements of pulmonary vascular distensibility in intact animal or man have not yet become practical or reliable (71, 293).

These generalizations about pulmonary vascular distensibility help to explain some physiological features of the pulmonary circulation. For example, the small pulse pressure in the pulmonary artery seems to be a consequence of both the marked distensibility of the pulmonary arterial tree, which prevents a considerable rise in pressure as the right ventricular stroke volume is ejected, and the low pulmonary vascular resistance, which allows more blood to escape from the pulmonary arterial tree during each systole and causes the pressure to fall earlier during systole (102, 182). The greater distensibility of the pulmonary than the systemic arterial tree also helps to account for the slower velocity of the pulse wave in the pulmonary artery (250 cm/sec) than in the aorta (300 cm/sec).

The unusual distensibility of the small pulmonary vessels, i.e., of the pulmonary "resistance" vessels affects their hemodynamic behavior. For example, as the pulmonary blood volume is expanded (251, 437), small pulmonary vessels share in this increase, leading to an increase in their transmural pressures, passive dilatation of their lumens and a decrease in their resistance to blood flow; since the arterial, capillary and venous portions of the small pulmonary vessels have different capacities and pressure-volume characteristics, the increase in pulmonary blood volume will not be equally apportioned among these vascular segments. Moreover, the distensibility characteristics and capacities are such that at low pulmonary vascular volumes and pressures, each increment in blood volume will raise the blood pressure less, and passively dilate the vessels more, than at high levels. This hemodynamic behavior is particularly relevant to those experiments in which an understanding of the passive characteristics of the pulmonary vascular tree and of its segments is prerequisite for interpreting a change in calculated pul-

monary vascular resistance in terms of pulmonary vasomotor activity (69, 101).

Resistance: Pressure-Flow Relationships

It has been noted above that, for the sake of expediency, flow through the pulmonary circulation is conventionally treated as though it were steady. Accordingly, and by analogy with Ohm's law, the ratio of the drop in mean pressure across the pulmonary circulation ($\overline{\Delta P}$) to the mean blood flow (\overline{Q}) is used as a measure of pulmonary vascular resistance. This idea of resistance is unambiguous when applied to rigid tubes perfused by a homogeneous fluid flowing in a laminar stream: under these special conditions, the plot of $\overline{\Delta P}$ against \overline{Q} is linear and passes through the origin, i.e., it is predictable and interpretable in physical terms. Complexities are introduced when these concepts are extended to the pulmonary (as well as to the systemic) circulation: the vascular bed is a nonlinear, visco-elastic, frequency-dependent system perfused by a complicated non-Newtonian fluid; moreover, the flow is pulsatile so that inertial factors, reflected waves, pulse wave velocity, and interconversions of energy become relevant considerations (156, 277). In such a system, resistance varies with pressure and flow; plots of $\overline{\Delta P}$ against \overline{Q} are not linear and do not pass through the origin (61, 169, 175). And, as the result of the many different active and passive influences which may affect the relationship between $\overline{\Delta P}$ and \overline{Q} , the term "resistance" is bereft of its original physical meaning: instead of representing a fixed attribute of blood vessels, it has assumed physiological meaning as a product of a set of circumstances.

TABLE 1. *Representative Values for a Normal Human Subject in the Basal State*

| | |
|-------------------------------|-----------------------------------|
| Pulmonary blood flow | 6.0 liters/min |
| | 3.1 liters/min/m ² BSA |
| Pulmonary blood pressures | s/d,m |
| Right atrium | 3/2,2 mm Hg |
| Right ventricle | 20/0 mm Hg |
| Pulmonary artery | 20/9,15 mm Hg |
| Pulmonary wedge | 6 mm Hg |
| Left atrium | 7/3,5 mm Hg |
| Pulmonary vascular resistance | 0.1* R units† |

* Calculated from the data in this table: $R = (15 - 5)/(6000/60) = 0.1$ R units. † R units express calculated resistance as mm Hg/(ml/sec); to convert to C.G.S. units (dynes sec cm⁻⁵), the value in R units is multiplied by 1328.

Meaning of Pulmonary Vascular Resistance

Generally speaking, the pulmonary circulation—which receives the same blood flow as the systemic circulation at one-fifth the blood pressure—is a low-resistance circuit. In the normal pulmonary circulation, the pulmonary vascular resistance is ordinarily of the order of 0.1 to 0.3 R units (table 1). But in evaluating data for resistance, at least three separate problems are involved: 1) the precise measurement of the parameters involved in the equation for resistance, i.e., pressure drop across the pulmonary vascular bed divided by the rate of pulmonary blood flow; 2) the decision as to whether a change in calculated resistance means a change in pulmonary vascular caliber; and 3) the interpretation of a change in caliber in terms of the mechanism which effected it, i.e., vasomotor or passive (61, 132).

With respect to the values substituted in the equation for resistance, it is self-evident that calculations of pulmonary vascular resistance, which are to be meaningful in vasomotor terms or even in terms of vascular caliber, presuppose accurate measurements of blood flow and pressures. Under certain stressful conditions, such as exercise, acute hypoxia, and acute hypercapnia, heightened respiratory excursions complicate the precise measurement of pressures, and pulmonary blood flow is easily miscalculated. Moreover, Permutt and co-workers have recently likened the pulmonary vessels to a series of Starling valves and warned against blind faith in the left atrial (or pulmonary venous) pressure as a measure of pulmonary outflow pressure. In particular, they have stressed that any situation in which alveolar pressure exceeds pulmonary venous pressure, by creating a discontinuity in pressure between the capillaries and the pulmonary veins, invalidates the use of the pulmonary venous pressure for the calculation of total pulmonary vascular resistance (315, 354). Accordingly, just as the studies of West *et al.* (427) suggest a spectrum of ventilation-perfusion relationships in the lung of upright man, the model of Permutt *et al.* (unpublished observations) suggests a distribution of the determinants of resistance to perfusion, depending on the relationships of pulmonary arterial, left atrial, and alveolar pressures in the different parts of the upright lung. The precise relationships between the normal imbalances between ventilation and perfusion on the one hand, and the interplay of alveolar and pulmonary vascular pressure on the other, remain to be elucidated.

With respect to the second problem, i.e., the equa-

tion of a change in calculated pulmonary vascular resistance to a change in pulmonary vascular calibers, there are at least two different types of enigmas. One is the possibility that a change in "anomalous viscosity," which is customarily disregarded, may masquerade as a change in caliber (197, 260, 430); since this source of confusion is most apt to become appreciable when pulmonary blood flow drops to exceedingly low levels, the practice of ignoring it seems reasonable as long as levels of pulmonary blood flow are of the same order of magnitude as that ordinarily encountered *in vivo*. The other is the equivocal anatomical meaning of a change in caliber, since a change in geometry may arise not only from a change in the diameters of patent vessels but also a change in the number of parallel paths which are being perfused (267).

Finally, before pulmonary vasomotricity can be invoked, it is axiomatic that all conceivable passive mechanisms for affecting vascular calibers (table 2) be taken into full account. One such passive mechanism, particularly likely during artificial ventilation, is the mechanical distortion of the vessels by adjacent lung tissue at abnormal lung volumes (397). Another, more universal, source of confusion is an undetected change in transmural pressure operating subtly to

TABLE 2. *Factors Conceivably Involved in a Change in Pulmonary Vascular Resistance*

| MECHANICAL (PASSIVE) | |
|-------------------------------------------|--------------------------------------------------------------|
| <i>Passive cardiocirculatory effects</i> | |
| 1. | Back pressure from left atrium or pulmonary veins |
| 2. | Change in pulmonary blood flow |
| 3. | Change in pulmonary blood volume |
| 4. | Bronchial collateral circulation |
| a) | Nutrition of nerves, ganglia, and smooth muscle |
| b) | Patency of collateral circulation |
| <i>Passive respiratory effects</i> | |
| 1. | Change in alveolar pressures |
| a) | Tone of bronchial smooth muscles |
| b) | Secretions of bronchial glands |
| c) | Alveolar surface tensions |
| 2. | Change in intrathoracic pressures |
| 3. | Tone of interstitial smooth muscle |
| 4. | Pericapillary edema |
| VASOMOTOR (ACTIVE) | |
| <i>Originating from without the lungs</i> | |
| 1. | Autonomic nervous system (including systemic chemoreceptors) |
| 2. | Catecholamines |
| <i>Originating within the lungs</i> | |
| 1. | "Critical" closure of small muscular vessels |
| 2. | Intravascular chemoreceptors |
| 3. | Chemical stimuli (directly on vascular muscle) |
| 4. | Deranged vascular metabolism |
| 5. | Local reflexes |

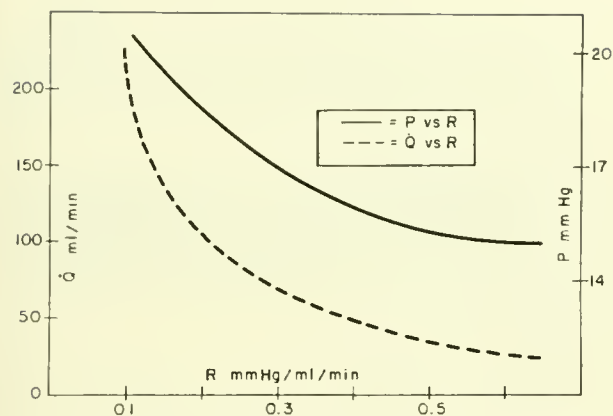


FIG. 31. Passive changes in pulmonary vascular resistance (R) at different pulmonary arterial pressures (P) and at different pulmonary blood flows (\dot{Q}). Pulmonary venous pressure remains constant throughout. As flow and pressure decrease, resistance increases. [Based on Edwards (119).]

modify vascular caliber and resistance. For example, an increase in transmural pressure—arising from an increase in either pulmonary arterial or left atrial pressure—passively widens the vessels and decreases their resistance (fig. 31); conversely, a drop in transmural pressure increases vascular resistance (36, 69, 366). Consequently, a change in resistance is not a reliable sign of pulmonary vasomotricity when transmural pressures change. Indeed, at different levels of transmural pressure, calculated resistance may remain unaltered even though pulmonary vasomotor tone has altered considerably (61). Considerations such as these have had two major effects on experimental design and interpretation: *a*) many have urged that the use of ohmic resistance be abandoned in favor of more straightforward presentation of pressures and the corresponding flows, and *b*) others have insisted on stringent experimental criteria, such as constant flow (fig. 31), left atrial, alveolar and intrapleural pressures before interpreting a change in pulmonary arterial pressure.

Practical Recognition of Pulmonary Vasomotricity

Dissatisfaction with the use of calculated resistance (a ratio) to detect an active change in vascular caliber has encouraged the use of graphic representations which relate blood flow to the pressure gradient that effects it (70). For example, the recognition of pulmonary vasomotor activity has been attempted by: *a*) the comparison of experimentally determined pulmonary vascular pressure-flow points, obtained after applying a stimulus, with the pressure-flow curve

which would be expected to obtain were it not for the stimulus (fig. 32); and *b*) the continuous registration of the pressure gradient across the pulmonary vascular tree and of the systemic blood pressure, before and after the injection of a pharmacological agent into the pulmonary artery (fig. 33).

The use of pressure-flow points to recognize vasomotor activity requires that the passive pressure gradient-flow relations be known or predictable. It is difficult to compare the published relationships in the pulmonary with those in the systemic circuit because conventionally the data do not cover the same range. Pressure-flow plots for systemic beds include zero pressure and zero flow, while the conventional presentation of pulmonary data start with "normal" pressure and flow and plot the fractional excess of one against the fractional excess of the other. Qualitatively, the

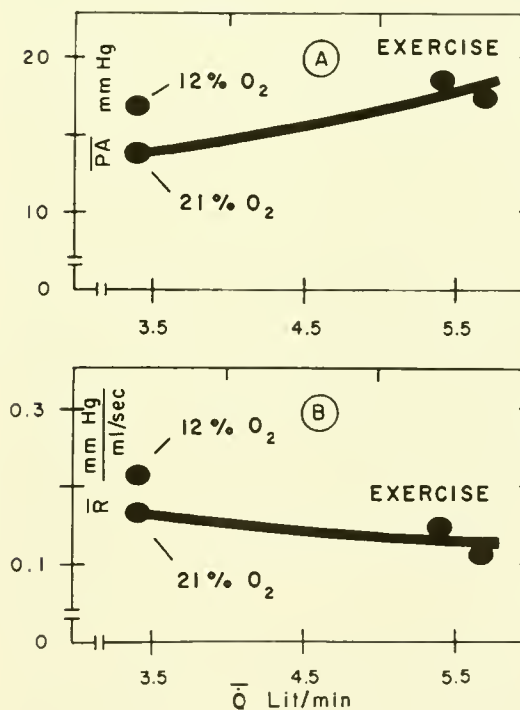


FIG. 32. Detection of a decrease in pulmonary vascular caliber from pulmonary arterial flow-pressure curves and from pulmonary vascular flow-resistance curves. For these curves, mild exercise was used to increase pulmonary blood flow passively and acute hypoxia was used as the test stimulus. *A*. During exercise, pulmonary arterial pressure increased as blood flow increased; during acute hypoxia, an equivalent increase in pressure occurred without an appreciable increment in blood flow. *B*. During exercise, calculated resistance decreased; conversely, during acute hypoxia, calculated resistance increased even though blood flow (and presumably all other respiratory and circulatory parameters) remain unchanged. [Based on Fishman *et al.* (132).]

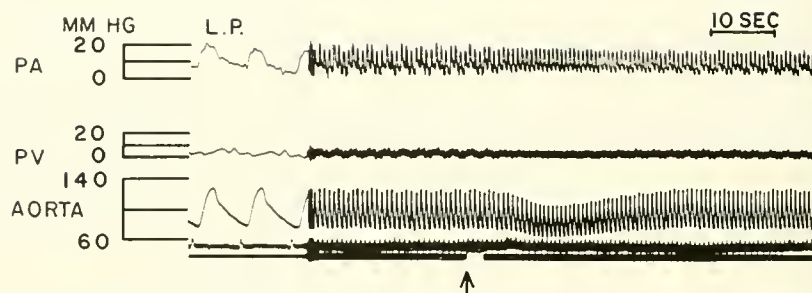


FIG. 33. Blood pressures in the pulmonary artery, pulmonary vein, and aorta following the injection of 5 mg of acetylcholine into the pulmonary artery of a human subject during open thoracotomy. The time of injection is indicated by the upright arrow. (Unpublished observations of A. G. Jameson and A. P. Fishman.)

lower portion of the pulmonary arterial pressure-flow curve in the rabbit (416), the dog (119, 252, 434), and man (89) resembles that of systemic beds: an increase in pressure is associated with a parabolic increase in flow; the inscribed curve is convex to the pressure axis. The upper portion of the pulmonary plot shows an opposite inflection which does not appear in systemic beds. Quantitatively, the pulmonary and systemic arterial curves differ not only in the level of the arterial pressure but also in the large increments in blood flow evoked by slight increments in pulmonary arterial pressure (at constant left atrial pressure).

Curves depicting the relationship between the driving pressures and flow are difficult to establish for either intact dog or man since it is impractical to increase pulmonary blood flow without simultaneously modifying the behavior of the respiration, the heart, and the systemic circulation. However, Lategola has succeeded in drawing a passive pressure-flow curve for the pulmonary vascular tree of the intact dog, using values obtained in the course of graded occlusion of the pulmonary arterial tree by balloon-tipped catheters (252). This curve appears as the solid line in figure 34. The shape of this curve is generally interpreted as showing that: *a*) as flow increases, resistance decreases; and *b*) beyond a transition phase ($\Delta\dot{Q}$ of approximately 250 per cent), resistance becomes constant. Moreover, the length of the gently sloping portion of the curve is regarded as a measure of the maximum calibers, both of the patent vessels and of those available to open in parallel; the start of the steeply ascending portion is thought to occur when the system begins to behave as though it were comprised of rigid tubes (89, 252). It should be noted that while the general shape of the pressure-flow relationship seems beyond cavil, the precise levels of flow at which the tubes appear to become rigid are not as

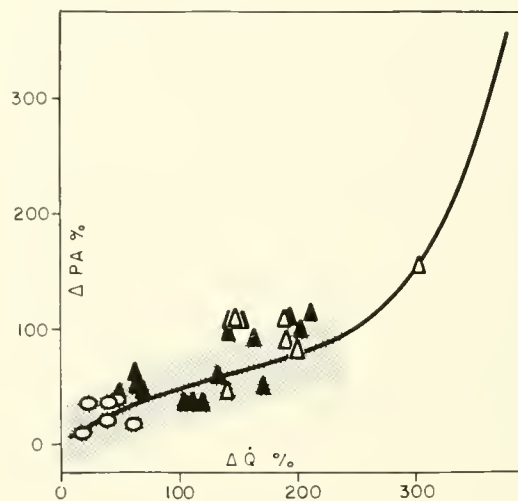


FIG. 34. Relationship between pulmonary blood flow and pulmonary arterial pressure in dog and man. Note that the origin represents normal or control levels (not zero levels) of both pressure and flow. The line is redrawn after Lategola (252) and is based on data obtained during graded occlusion of the pulmonary artery tree in the dog. The shaded area represents corresponding measurements in normal man during balloon occlusion of one pulmonary artery both at rest and during mild exercise (42). The individual points represent observations on human subjects during supine exercise. *Open circles*: mild exercise (382); *solid triangles*: graded exercise (149); *open triangles*: mild exercise after pneumonectomy (89).

convincingly established (281) and the final slope must be considered in the assessment of constancy of resistance.

Superimposed on the pressure-flow curve of the dog is a shaded envelope which includes the points obtained during similar occlusion of a pulmonary artery in man (42); in order to exceed the increments in blood flow obtainable at rest, the human subjects performed mild leg exercise during the occlusion of one pulmonary artery. It may be seen that the envelope of human points closely follows the horizontal

portion of the dog's pressure-flow curve; unfortunately, in this study, sufficiently high flows to define the steep portion of the curve were not achieved. However, the original measurements by Cournand and co-workers on human subjects after pneumonectomy (open triangles) suggest that the rest of the human pressure-flow curve may also resemble that of the dog (89). More observations in both man and dog at higher levels of flow are obviously needed; unfortunately, patients with congenital left-to-right shunts, who may, from a priori considerations of their large pulmonary blood flows, appear to be logical candidates for such measurements, are usually found to be unsuitable for pressure-flow curves because of complicating pulmonary vascular disease and anatomical defects which preclude precise measurements of pulmonary blood flow.

There are three interesting side lights to the curve illustrated in figure 34. The first is the difference between this parabolic curve of the normal subject and the linear relationship between pressure and flow which has been described for patients with abnormal vascular beds (132); this difference suggests that those animal or isolated-lung experiments which find a linear relationship between pulmonary arterial pressure and flow may be dealing with abnormal, or overfilled, lungs (132). The second is the relationship between the sharp inflection of the curve and the maximum diffusing capacity; it has yet to be established whether maximal dilatation of the pulmonary capillary bed, i.e., the achievement of the maximum diffusing capacity, coincides with the abrupt increase in the pulmonary arterial pressure (267, 407). The third deals with the use of graded exercise to construct the pressure-flow curve in intact animal or man. It may be seen that during mild to moderate exercise in man, the pressure-flow points overlap those obtained during graded occlusion in the dog; during heavier exercise, the coincidence of human and animal points is not as exact. These discrepancies raise the possibility that strenuous exertion may sufficiently alter passive determinants, i.e., transmural pressures and left atrial pressure, to invalidate the use of such exercise for the construction of a reference curve which is supposed only to depict the uncomplicated consequence of increasing flow on pressure (132). On the other hand, the use of mild to moderate exercise for this purpose seems valid on several scores: *a*) the mean left atrial pressure (104) and mean pleural pressures are little affected by light exercise (132), *b*) the pressure-flow curves obtained during light exercise and the passive curves obtained from iso-

lated lungs are quite similar (119, 416), and *c*) the exercise points correspond to those obtained during graded occlusion of the pulmonary artery (42, 53, 101).

The second way of identifying pulmonary vasoconstriction is particularly applicable to the use of pharmacological agents; it has the advantage of circumventing many of the restrictions outlined for steady-state measurements. It involves (fig. 33) the single injection of a pharmacological agent into the pulmonary circulation of the intact animal or man and the continuous registration of the pressure drop across the lungs, the heart rate, and the systemic blood pressure during the single pulmonary circulation, i.e., before recirculation. In this way, the effect of the agent appears as a change in pulmonary arterial pressure before flow can change and before the agent can affect the systemic circulation (187). An alternate way of accomplishing the same end for steady-state experiments is the continuous infusion of an agent, e.g., acetylcholine (192, 441) which is destroyed within the lungs during the course of a single circulation.

Blood Flow Through Each Lung Separately

After application of a unilateral stimulus, such as hypoxia (135), or the unilateral infusion of acetylcholine (89), the partition of flow between the two lungs is a measure of the relative resistances of the two sides since the pressure gradient across the lungs is identical on the two sides. Although the idea of using one lung in this way, as a control for the other, is intuitively attractive, the experiments are generally technically difficult, particularly if bronchspirometry is involved.

Critical Closure

Small muscular blood vessels of the systemic circulation are believed to be inherently unstable so that they are inclined to spring shut—concentrically and completely—when their intraluminal pressure drops below a critical value. This “critical closing pressure” has been proposed as a measure of the tone of vascular smooth muscle, i.e., of vasomotor activity: the level of the “critical closing pressure” increases as wall tension increases and as the size of the vessel decreases. Critical closing pressure is manifested experimentally by the arrest of flow despite an appreciable perfusion pressure. By similar reasoning, the muscular small vessels spring open when “critical opening pressures” are exceeded (60, 165).

The concept of critical opening and closure has been invoked to account for certain puzzling responses of the pulmonary circulation (429). These include the exceedingly gradual increase in pulmonary arterial pressure during graded exercise (267), the relative stability of the pulmonary arterial blood pressure during hemorrhage (160), and the pressure gradient between the pulmonary artery and left atrium as the left atrium falls below 7 mm Hg (36, 366).

However, it is more difficult to prove the operation of critical opening and closure of small vessels in the pulmonary, than in the systemic, circulation. The difficulties are of several different kinds: *a*) mechanical influences, e.g., local changes in transmural pressure, may open and close vessels independent of vasomotor activity; *b*) the effects of anomalous viscosity are apt to be more pronounced and to simulate changes in vascular calibers in a low-pressure circulation; *c*) the pulmonary arterioles are thin-walled, wide-lumened and, in general, poorly constructed to spring shut; *d*) there are generally alternate, and equally convincing mechanisms to account for pulmonary vascular behavior (272); and *e*) experiments specifically designed to look for signs of critical closure have not always been able to find them (273, 434).

At present, the experimental evidence for critical opening and closure of small pulmonary vessels—a vasomotor phenomenon—is inconclusive. If the phenomenon does occur, it seems to do so when the pressure gradient between the pulmonary artery and left atrium is exceedingly low, i.e., of the order of 1 to 2 mm Hg (42); moreover, it does not seem to affect equally all small vessels of comparable dimensions (273, 366). In general, transmural pressures are more apt to be involved in the closure and opening of small pulmonary vessels than is vasomotor activity. It would be of interest to examine such closed pulmonary vessels to see if their lumens are slits (mechanical collapse) or circles (concentric obliteration by vasoconstriction).

Potential and Kinetic Energy

Mechanical energy is imparted by the right ventricle to the blood perfusing the pulmonary circulation in two forms, kinetic and potential energy. At rest, the kinetic energy factor in the pulmonary circulation is of the order of 10 per cent or less of the total; on the other hand, both in normal subjects during exercise and in patients with pulmonic stenosis or left-to-right shunts, the kinetic energy factor may increase to over 50 per cent of the total (320, 338).

The usual calculation of resistance deals only with the drop in potential energy (pressure) across the system. It does not take into account the fact that as blood courses down the pulmonary vascular tree, part of the kinetic energy is reconverted to pressure energy as the area of the bed increases; a small fraction is dissipated as heat arising from the friction of blood flow (20). In experimental pulmonic valvular insufficiency, the unusually rapid blood flow and turbulence in the pulmonary artery may produce a drop in pressure across the pulmonic valve (123).

These considerations suggest that at rest, when the kinetic energy factor is small and of the same order of magnitude in the pulmonary arteries and veins, the drop in potential energy (pressure) between the pulmonary arteries and veins provides a rough measure of the decrease in mechanical energy across the pulmonary vascular bed; on the other hand, in normal subjects during exercise, and in patients with cardiac abnormalities characterized by large stroke volumes and rapid rates of pulmonary blood flow, the pressure gradient across the pulmonary circulation does not provide an adequate measure of the mechanical energy delivered to the system.

PULMONARY CAPILLARY CIRCULATION

Pulmonary Capillary Pressure (P_c)

Since a direct method for measuring P_c pressures is not available, the level of the P_c pressure is generally estimated from the pulmonary arterial diastolic pressure on the one hand, and the mean left atrial pressure, on the other. In the normal subject these limits set the mean P_c pressure at approximately 10 mm Hg.

Rate of Pulmonary Capillary Blood Flow (\dot{Q}_c)

In the normal animal or man the rate of pulmonary capillary blood flow is virtually identical with the right ventricular output; in left-to-right shunts or extensive collateral arterial circulations, \dot{Q}_c exceeds the right ventricular output. An earlier chapter has analyzed the methods used to measure the cardiac output. Of special interest to the present section is the use of inert soluble gases not only to measure the rate of pulmonary capillary blood flow in man but also to explore the nature of the pulmonary capillary flow. Throughout this section it will be assumed that physiological measurements of pulmonary capillary

flow need not be measuring only the flow through anatomic pulmonary capillaries. The physiologic measurements may also be including the flow through other small pulmonary vessels that participate in the uptake of the inert gas. However, this distinction between the anatomic and the physiologic pulmonary capillary is more meaningful with respect to relating the gas-exchanging characteristics of the small pulmonary vessels to their hemodynamic behavior than with respect to the measurement of the cardiac output.

The principle underlying the use of inert gases to measure pulmonary blood flow was enunciated by Bornstein in 1910 (343). Unfortunately, he chose an insoluble gas, i.e., nitrogen, as the test gas. In 1912, Krogh & Lindhard (240) substituted the soluble inert gas, nitrous oxide, for nitrogen and devised an experimental protocol, involving respiratory maneuvers, to obtain the values needed for the equation,

$$\dot{Q}_c = \dot{V}_{N_2O} / \lambda N_2O \cdot \bar{F}_{AN_2O}$$

in which \dot{Q}_c = pulmonary capillary blood flow per minute

\dot{V}_{N_2O} = volume of N_2O absorbed per minute (BTPS)

λN_2O = Ostwald's coefficient of solubility of nitrous oxide in blood at 37°C

\bar{F}_{AN_2O} = mean fraction of N_2O in alveolar gas during the test (BTPS).

Since the coefficient of solubility (λ) is constant, the variables involved in the calculation of the flow are two: 1) the volume of N_2O absorbed per minute (\dot{V}_{N_2O}); and 2) the mean alveolar fraction of N_2O during the test (\bar{F}_{AN_2O}). Subsequently, it was shown that there are several practical limitations to the Krogh and Lindhard method; these include: a) the need to complete the test before recirculation of the test gas; in normal man the pulmonary recirculation time is of the order of 11 ± 3 sec (74, 343); b) the difficulty in obtaining simultaneous measurements of the different variables involved in the equation; c) the dilemma of distinguishing the uptake of the gas by the pulmonary tissues from the uptake by the pulmonary capillary blood; and d) the unsubstantiated use of "correction factors" (273, 343). Despite these reservations, the inert-gas methods do provide accurate measurements of pulmonary capillary blood flow (\dot{Q}_c) in resting subjects if proper precautions are taken. However, during exercise and in chronic pulmonary disease they become less reliable. The current consensus appears to be that despite the

attractive simplicity of these tests, their most reliable use, even in resting patients with normal lungs, is for consecutive measurements of \dot{Q}_c .

Interest in the use of soluble, inert gases to measure pulmonary capillary blood flow lagged once the direct Fick and Stewart-Hamilton methods were standardized into clinically useful techniques. However, it revived when Lee and DuBois substituted the body plethysmograph for the spirometer to measure the rate of uptake of nitrous oxide: this ingenious modification of the Krogh and Lindhard method promised not only to provide the usual measure of the rate of capillary blood flow per minute but also of the rate of flow at any instant (254). Unfortunately, there are practical difficulties inherent in the use of the body plethysmograph for the measurement of instantaneous flow. These limitations have led to the development of modified plethysmographic techniques in man (37, 418) and a modified cardiopneumographic method in the dog (185, 298).

Nature of Pulmonary Capillary Blood Flow

Whether pulmonary capillary flow is steady or pulsatile is critical for the understanding of both pulmonary hemodynamics and gas exchange (275, 319). For example, if the linear velocity of the blood flow through the alveolar capillaries were to vary during the cardiac cycle without compensatory changes in other parameters, e.g., diffusing capacity and capillary blood volume, the equilibration between alveolar gas and capillary blood might well be disturbed (143).

A standard of reference for assessing the nature of the pulmonary capillary blood flow is the prevalent idea that blood flow through the systemic capillaries is ordinarily continuous and devoid of major oscillations from the mean. This idea is consistent with two features of the systemic circulation: a) the interplay between arterial distensibility and arteriolar resistance, so that the systemic "windkessel" maintains flow during diastole; and b) the varying path lengths between the root of the aorta and the capillaries. Of these two influences, the windkessel effect is held to be the more important.

It is much more difficult to predict the nature of the pulmonary capillary flow. On the one hand, marked surges of capillary flow following systole (pulsatile flow) might be expected to occur on at least two accounts: 1) the relatively small capacity of the pulmonary arterial tree as compared to the systemic arterial tree; and 2) the relatively low re-

sistance of the small precapillary vessels (102). On the other hand is the fact that, somewhere en route to the pulmonary veins, the pulmonary arterial pressure pulse is damped out so that the pulmonary venous pressure pulse ordinarily reflects only left atrial events. The problem then devolves into deciding the degree to which the flow pattern in the pulmonary capillaries resembles the pattern of instant-to-instant changes in the pulmonary vascular pressure gradient and of flow in the pulmonary artery.

If it is assumed that the pattern of pulmonary capillary blood flow is uniform throughout the lung, direct inspection of the surface capillaries of the lung should afford some insight into the nature of the pulmonary capillary flow. In 1733, while examining the exposed frog lung, Stephen Hales observed that not only was blood "sensibly accelerated at each systole in the finest capillaries, but also in their corresponding capillary veins, tho' not in their larger trunks" (178). This was the first declaration that pulmonary capillary flow—at least in the frog—was pulsatile. However, 200 years later, observations on transilluminated lung of the cat indicated that the pattern of capillary flow in the mammalian lung was distinctly different from that of the amphibian lung; thus, instead of pulsatility, Wearn and co-workers stressed intermittency, a phenomenon attributable to the opening and closing of pulmonary precapillary vessels (419). The rarity of pulsatile flow in the surface capillaries of the mammalian lung has since been confirmed by others (21).

Opposed to these direct observations on the mammalian lung are the results obtained by plethysmographic techniques in man (37, 254, 418). Not only do they picture pulmonary capillary flow as regularly and vigorously pulsatile, but they also depict a flow pattern in the pulmonary capillaries which corresponds more closely to the instantaneous changes in the blood pressure gradient across the lungs than to the flow pulse in the pulmonary artery (fig. 29) (270). Moreover, unless one postulates species differences among mammals, these results in man also challenge the notion that examination of the surface capillaries of the lung is a useful index of the pattern of flow in the bulk of the pulmonary capillaries.

Even though the majority of the plethysmographic studies agree that pulmonary capillary blood flow is pulsatile in man, they are not entirely consistent with respect to the form of the capillary flow pulse. For example, not only do the published records differ with respect to the amplitude of peak flow,

but they also display different contours for the flow pulse: some, but not all, the records indicate that flow is interrupted for much of each cardiac cycle; often, pulmonary capillary blood flow seems to reverse; finally, the reported flow patterns generally vary from beat-to-beat. Undoubtedly, at least part of this variability is attributable to practical difficulties inherent in the plethysmographic techniques (342). In addition, as may be gleaned from figure 35, inaccuracies are inescapable in the matching and analysis of the air and nitrous oxide records.

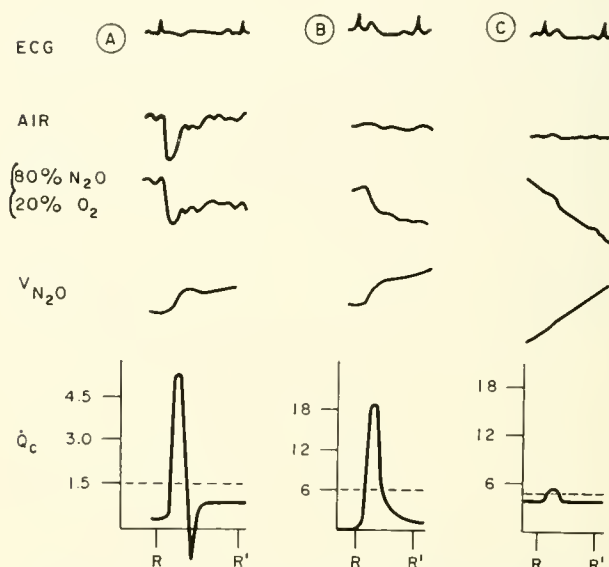


FIG. 35. The pattern of the pulmonary capillary blood flow according to the pneumocardiographic (A) and plethysmographic (B and C) methods. From above downward, the electrocardiogram (ECG), the air record (AIR), the nitrous oxide record (80% N_2O , 20% O_2), the difference between the air record and the nitrous oxide record (V_{N_2O}), and the rate of pulmonary capillary blood flow (\dot{Q}_c) in liters per minute. A: actual pneumocardiograms obtained from an anesthetized, curarized dog during arrested respiration. Mechanical events are eliminated in the process of point-by-point subtraction of the nitrous oxide pneumocardiogram from the air pneumocardiogram, yielding a record of instantaneous changes in airway pressures due only to the volumes of nitrous oxide removed by the perfusing blood (V_{N_2O}). Differentiation of the volume-uptake record provides a record of the rate of uptake of nitrous oxide and, therefore, of the pulmonary capillary blood flow (\dot{Q}_c). Except for the unexplained dip in the \dot{Q}_c record, pulmonary capillary flow appears to be continuous and largely confined to the systolic portion of the cardiac cycle. B and C: hypothetical plethysmographic records to compare strongly pulsatile but continuous capillary flow (B) with weakly pulsatile but continuous capillary flow (C). Not illustrated is the possibility of interrupted capillary flow, i.e., that capillary flow may actually stop (drop to zero) for part of each cardiac cycle. [After Morkin *et al.* (298).]

Size of Pulmonary Capillary Bed

Although the extent of the pulmonary capillary bed in a living subject cannot be expressed in absolute units, a change in area can be detected from consecutive measurements of the pulmonary diffusing capacity. Such measurements, using either oxygen or carbon monoxide as the test gas have shown that: *a*) not all of the available area is in use at rest; and *b*) the capillary area involved in gas exchange increases progressively under a variety of circumstances, e.g., exercise. The major mechanism involved in increasing the area is an increase in transmural pressure (357). The precise way in which this distending pressure is increased varies from circumstance to circumstance. Thus, in some conditions, an increase in capillary blood volume is involved; in others, the perivascular pressures may decrease; at high lung volumes, the capillaries may even be passively stretched. As expected from theoretical considerations, the diffusing capacity is little affected by changes in pulmonary blood flow; only when pulmonary blood flow is severely curtailed does the diffusing capacity decrease (358, 407). Pneumectomy generally (143), but not invariably (89) decreases the diffusing capacity.

The maximum diffusing capacity is of interest as a measure of the maximum available pulmonary capillary area. It has been suggested that this maximal value is reached at a level of blood flow which corresponds to the steep inflection of the flow-pressure curve (fig. 34). However, the experimental support for this hypothesis is inconclusive (348).

Pulmonary Capillary Blood Volume (Q_c)

On the basis of measured differences between the rates of reaction of carbon monoxide with hemoglobin solutions at different oxygen tensions, and the calculation of the average time spent by blood in traversing the pulmonary capillaries, the volume of blood in the pulmonary capillaries of the normal resting subject was originally calculated to be of the order of 60 to 75 ml (364, 365); during severe exercise, Q_c increased somewhat (to approximately 90 to 100 ml) (223, 364). More recent measurements and calculations of the same type have raised the value of the resting Q_c to approximately 100 ml, both for the normal subject (15, 244) and for the patient with mitral stenosis (15). At present, there is no way to decide how much of the reported variability is artificial (143, 365) and how much is a consequence of either

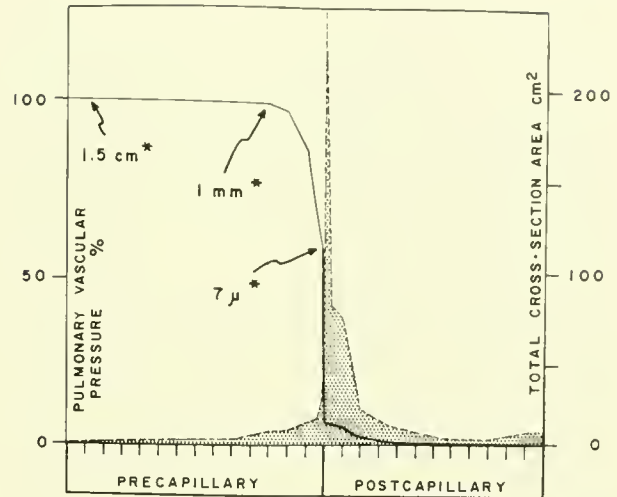


FIG. 36. Hypothetical relationship between blood pressure (solid line) and cross-sectional area (shaded) in the pulmonary vascular bed of the dog. The blood pressure is represented as per cent of initial value. Vascular diameters at key points are indicated by asterisks. According to this schema, the major drop in blood pressure occurs in the region of the pulmonary capillaries (shaded spike). [Based on Schleier (373).]

biological differences between subjects or the effects of the breathing maneuvers which are part of the tests (244). A variety of agents and procedures seem to be capable of passively altering Q_c (262).

In the dog, anatomical measurements suggest that the pulmonary capillaries may contain 10 per cent of the total volume of blood between the right ventricle and left atrium, i.e., of the order of 1.2 per cent of the total circulating blood volume (169). For the human lung, Weibel found that Q_c varies with the lung volume and with the degree of capillary filling. In his preparation, which involved negative (pleural) pressure inflation of the lung and fixation in formalin vapor, Q_c was 150 to 200 ml, i.e., approximately twice the volume obtained by physiological measurements. Part of the difference between the anatomical and physiological measurements may be the degree of inflation of the lung (422).

Resistance and Distensibility

How much of the pulmonary vascular resistance to perfusion lies in the pulmonary capillary bed is a matter of opinion (66). The prevalent notion is that, under ordinary conditions, the resistance function resides in the small, muscular precapillary vessels. On the other hand, calculations of resistance based on anatomical measurements and assumptions have raised the possibility that a large part (up to half) of

the pressure drop across the pulmonary vascular bed may occur in the capillaries (fig. 36) (373). Consistent with the latter view are some physiological observations on the isolated lung (318). While such calculations and observations cannot define the major site of pulmonary vascular resistance under natural conditions, they do emphasize that the evidence favoring the precapillary segments is not on firm footing.

Under certain circumstances, the capillaries do become the major site of pulmonary vascular resistance. The most common circumstance is the artificial increase in alveolar pressure in the course of positive pressure breathing (191, 306). It is also possible to imagine such a role for the capillaries in those natural circumstances in which the left atrial pressure happens to fall below alveolar pressures. Such a condition presumably exists in the apical alveoli of the upright human subject and is exaggerated when the standing subject takes a deep breath.

In isolated lungs perfused at physiological levels of blood pressure, the pulmonary capillaries appear to be less distensible than the larger pulmonary vessels (124). However, physiologically meaningful measurements of the distensibility characteristics of the pulmonary capillaries are difficult to obtain for a variety of technical reasons, including the inaccessible location of the capillaries, the difficulty of making static measurements under *in vivo*, dynamic conditions, the difficulty in reproducing the natural capillary pressures in experimental preparations, and the uncertainty concerning the distensibility characteristics of the pericapillary tissues because of the propensity of the isolated lung to develop pulmonary edema.

Time Spent by Blood in Pulmonary Capillaries

Stephen Hales seems to have been the first (1733) to pay serious attention to the rate at which blood flows through the pulmonary capillaries; coupling direct observation with simple arithmetical calculation, he estimated this rate to be approximately 1.4 mm per sec in the frog lung (178). Curiously enough, the elaborate techniques of the twentieth century (cine-microphotography with lamp black as a tracer in the exposed lung) have provided similar values for the cat (1 to 2 mm/sec) (414).

The latter observations on the cat are the only direct observations on the time spent by particles in the pulmonary capillaries (0.1 sec). All other esti-

mates represent calculations and assumptions based on measurements of alveolar capillary gas exchange. The most commonly cited values are those of Roughton, based on the kinetics of the combination of carbon monoxide and hemoglobin in man. Originally, this approach indicated that, on the average, a unit of blood spends approximately three-quarters of a second in gas exchange in the pulmonary capillary at rest, and somewhat less during exercise (364); subsequent refinements in methodology have suggested that the contact time at rest may be a little longer, i.e., of the order of 1 sec (223, 317, 365). Other calculations, based on the analysis of the alveolar-arterial oxygen gradient have yielded lower values: 0.18 sec in the dog (295) and 0.23 to 0.5 sec in resting man (295, 396); however, theoretical considerations suggest that this approach tends to underestimate the time of contact (318). Finally, anatomical considerations have led to the low contact time of 0.1 sec (301). At first encounter, this is a discouraging span of values. But, in view of the wide variations in methodology, assumptions, and types of calculations, this range of about 0.1 to 1.0 sec in resting man is surprisingly small and, when duly weighed, the generally accepted value of three-quarters of a sec to 1 sec at rest seems quite reasonable. Obviously lacking are simultaneous measurements of contact time by the physiological methods and by direct observation of the exposed lung in the same animal (143).

The time spent by a unit of blood in the pulmonary capillary depends on various hemodynamic influences. Paramount among these is the relationship between the stroke output of the right heart and the pulmonary capillary blood volume; in resting man these two values are of the same order of magnitude. Another determining influence is the nature of the pulmonary capillary blood flow: pulsatile pulmonary capillary flow causes some red cells to spend less time in the pulmonary capillaries than others. Finally, values based on alveolar-capillary gas exchange and the rate of combination of test gases with hemoglobin may misjudge actual contact times; for example, actual time would be expected to differ from calculated time if, as is customarily done, the calculations assume that the hematocrit of pulmonary capillary blood is identical with that of blood sampled from large systemic vessels (143, 317).

These theoretical considerations may have practical meaning. Ordinarily, the time spent by each unit of blood in the pulmonary capillary is more than ample for complete oxygenation, both at rest and during

exercise. However, it is conceivable that, under certain pathological conditions, such as those which involve a huge pulmonary blood flow through a curtailed pulmonary vascular bed, the contact time may be too brief. Indeed, an inadequate contact time has been invoked to account for peripheral arterial hypoxemia in resting patients with multiple pulmonary emboli and in exercising patients with "alveolar-capillary block" (359). However, such explanations are not entirely convincing since, in most of these pathologic states, other equally convincing explanations for peripheral arterial hypoxemia, e.g., opening of pulmonary arteriovenous shunts, also exist.

Pulmonary Capillary Hematocrit

In the 1930's, Fåhræus and Lindquist pointed out that blood flowing in capillary tubing has a greater ratio of plasma to red cells than does blood in wider streams (18). Since then, it has been repeatedly shown that the hematocrit of blood in many organs is less than in the large vessels which enter and leave them. The lung appears to be no exception: measurements of the hematocrit of blood obtained from whole organ homogenates (161) as well as comparisons of transit time of tagged red cells and plasma (332) indicate that the small vessel hematocrit is regularly lower than that of the large vessels, ranging from 17 per cent less at rest to 13 per cent less during exercise. This difference may affect not only the hemodynamic behavior of the pulmonary capillary circulation but also measurements of alveolar-capillary gas exchange, such as the pulmonary diffusing capacity for carbon monoxide, and derivative values, such as the time spent by blood in the pulmonary capillary and the pulmonary capillary blood volume (143, 318).

Transcapillary Exchange

Until recently, considerations of the transcapillary movements of water and electrolytes emphasized their bulk transfer and dealt largely with the balances between hydrostatic and oncotic pressures (Starling's law of capillary exchange). Recognizing that the pulmonary capillaries were unique in being "bathed in air rather than in water," such considerations of bulk transfer were sufficient to account for the normal "dry" lungs as well as the "wet" lungs of clinical pulmonary edema. Within the last few years, transcapillary exchange by diffusion has also been taken into serious account (76). Still incomplete is the

definition of the role of the pulmonary lymphatics with respect to the water which escapes into the pulmonary interstitium and alveoli.

Certain aspects of the transcapillary exchange of water seem well established. For example, the osmotic pressure of the plasma colloids (expressed figuratively as an "oncotic pressure") of approximately 25 mm Hg normally suffices to prevent bulk loss of fluid from the pulmonary capillaries, even in the hydrostatically dependent portions of the lung. Also, while transcapillary molecular exchange rates by diffusion may be of the order of the cardiac output, no net fluid transfer occurs. Ethanol and injected carbon dioxide behave like isotopic water. As expected, the indicator-dilution curves for T-1824 (which does not leave the capillaries) and for water (which undergoes rapid to-and-fro transcapillary exchange) are quite different (76). Indeed, labeled water resembles the inert gases in behaving as though the barrier did not exist.

Quite unexpected is the similarity between the T-1824 indicator-dilution curve and the corresponding curves for urea and for the highly diffusible phosphate, potassium, sodium, and chloride ions (16, 77, 360). Virtual identity of these curves has been interpreted to mean that: *a*) in contrast to the enormous pulmonary volume of distribution of sodium and chloride at equilibrium (134), the volume of dilution available to urea and to the diffusible ions during a single circulation is confined either to the strict pulmonary vascular volume or to the pulmonary vascular volume plus an additional, circumscribed perivascular volume into which these substances diffuse and then promptly return, and *b*) because of the ready permeability of the barrier (probably the basement membrane) to water as well as its relative impermeability to ions and urea, the barrier is aqueous rather than lipid in nature.

MISCELLANEOUS HEMODYNAMIC PHENOMENA

Pulmonary Arterial Pulse-Wave Velocity

The pulse-wave velocity is related to relative, rather than to absolute, distensibility (see Chapter 24). Estimates of the speed at which the pulse wave travels along the length of the pulmonary arterial tree vary considerably. The discrepancies are attributable to three causes: inadequate methodology; the experimental difficulty of controlling the hemodynamic influences which modify the speed of the

pulse wave, e.g., initial volume or diastolic pressure; and species differences in distensibility. Thus, one set of values for the pulmonary arterial pulse-wave velocity in the rabbit averages 200 cm per sec (124); this method is based on measurements of pulmonary vascular distensibility and capacity. On the other hand, much lower values (83 cm/sec) have been calculated by an alternate approach which involves the registration of phase shifts of a single harmonic component of the pulse wave as it traverses a known distance (140a). Similarly, in the dog, mean velocities have averaged 250 cm per sec in one study (311) and 400 cm per sec in another (225). Finally, in man, kymographic studies have indicated a velocity of 200 cm per sec in the main pulmonary artery and 275 cm per sec in the peripheral branches (71). It should be noted that each of these methods has its own peculiar problems: thus, some are troubled by the need for the precise measurement of *in vivo* distances between points on the pulmonary artery (71, 225); others have to overcome the difficulty of attempting static measurements under dynamic conditions of flow (124).

Because of the practical limitations and assumptions involved in the experimental approaches, none of these values seem to offer more than an order of magnitude. However, with a single exception (225), they are consistent with the notion that the pulse-wave velocity in the distensible pulmonary arterial tree is somewhat less than in the aorta.

Pulmonary Circulation Time

Measurements of circulation times are in common clinical use for the recognition of heart failure. This use depends on the arrival of a test substance at a chosen site in sufficient concentration to be detected; the value obtained, i.e., the "appearance time," is related, in a complex way, to the mean circulation time used for the calculation of central blood volume (184, 313). It is clear that the precise value for circulation time will be influenced not only by technical peculiarities, e.g., by rate of injection, nature of the test substance, and sensitivity of the detector, but also by physiological events. For example, if the pulmonary circulation lies between the sites of injection and sampling, an increase in its blood volume will dilute the test substance excessively and delay its recognition at the test site. It is, therefore, not surprising that values for circulation times from different laboratories are frequently inconsistent.

One study in the dog (Stewart principle) found the

total circulation time to be approximately 11 sec, and the pulmonary circulation time to average approximately half of the total (184). Other studies indicate that the pulmonary circulation time (pulmonary artery to vein) is somewhat less, i.e., about 3 to 4 sec (306, 329). The circulation time for red

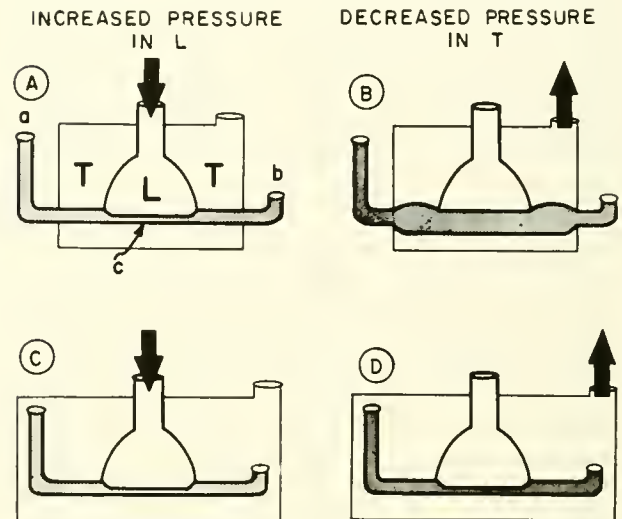


FIG. 37. Two-chamber model to illustrate the effects of varying pressures around a collapsible rubber tube on its dimensions. The tube (*a, c, b*) runs through one rectangular chamber (*T-T*) and is exposed for a limited extent (*c*) to the pressure of the other chamber (*L*). In *A* and *B*, the two ends of the perfusing system (*a, b*) are outside of the chambers; in *C* and *D*, the entire system is contained within chamber *T-T*. For the sake of clarity, only *A* has been lettered; the arrow in each figure indicates the chamber subjected to a change in pressure and the direction of change. *A*: the pressure in chamber *L* is greater than atmospheric; the pressure in chamber *T-T* is atmospheric. The aspect of the tube exposed to *L* is collapsed. *B*: the pressure in chamber *T-T* is less than atmospheric; the pressure in *L* is atmospheric. The whole length of tube within chamber *T-T* is increased in diameter; the portion exposed to *L* is less dilated than the remainder of the tube. *C* and *D*: two different but equivalent conditions. As long as the reservoirs are contained within chamber *T-T*, the same effect is obtained by balancing positive pressure in *L* against atmospheric pressure in *T-T* (*C*) or by balancing atmospheric pressure in *L* against negative pressure in *T-T* (*D*). In either case, the result is identical with that illustrated in *A*. By analogy, this model suggests that: 1) when alveolar pressure (*L*) is raised (1), the transmural pressure of adjacent vessels (*c*) is decreased, 2) the situation of two reservoirs (pulmonary arterial and venous pressures) outside of the pleural cavity (*B*) corresponds to negative (pleural) pressure inflation as well as to normal respiration, 3) when pleural pressure is decreased (*B*), the transmural pressures of larger vessels are increased more than those of the capillaries; and 4) the situation of two reservoirs in the pleural cavity (*C* and *D*) is a physical identity with positive pressure inflation. [Based on Quincke & Pfeiffer (324).]

cells is less than that of the plasma [cell transit time, plasma transit time = $0.91 \pm .05$ (310)]. In man, the total (systemic plus pulmonary) circulation time is of the order of 15 to 18 sec (184). Approximately, one quarter to one third of the total time is spent in traversing the pulmonary circulation; the circulation time between the right ventricle and the pulmonary capillaries is estimated to be 2 to 3 sec (87). Despite the many measurements of the pulmonary circulation time, both in normal subjects and in patients with cardiopulmonary disorders, there is still an inadequate fund of information concerning the precise pulmonary vascular pathways traversed by the test substance between the sites of injection and sampling (75).

INFLUENCE OF RESPIRATION ON PULMONARY CIRCULATION

In the pulmonary circulation, blood pressures, volume, and flow change during each breath. The precise nature of these changes has been debated for two centuries (50, 324). Nonetheless, many aspects remain unsettled largely because of the technical difficulties involved in simultaneously recording transient respiratory and circulatory events in the intact animal or man.

The attempts to circumvent the technical difficulties have created problems of their own: *a*) the recourse to simplifying physical models (fig. 37) and artificial preparations has led to dubious generalizations about natural breathing (61, 354); *b*) the experimental control of some respiratory influences at the expense of others, has tended to exaggerate the physiological importance of some parameters while denying others—such as the degree and type of inflation—their full due (215, 380); and *c*) complicated experimental designs have created artificial situations in which the usual calculation of pulmonary vascular resistance either does not apply or is very difficult to translate into terms of pulmonary vascular dimensions (315, 354).

Spontaneous Breathing

During inspiration, as pleural pressure becomes more negative, luminal pressure (referred to atmosphere) decreases. On the other hand, transmural pulmonary arterial pressures—systolic, diastolic, and mean—increase. During expiration, these changes are reversed.

There is no unanimity concerning the mechanisms responsible for the increase in pulmonary arterial transmural pressure during inspiration. Most certain is an increase in pulmonary blood flow, arising from the decrease in intrathoracic pressure and from the increase in systemic venous return which it promotes (17, 49); much more equivocal is a reduction in the outflow from the pulmonary vascular bed so that the pulmonary blood volume is increased (225, 253). Such a combination of increased inflow and reduced outflow would imply pulmonary vascular distension and, hence, a decrease in pulmonary vascular resistance.

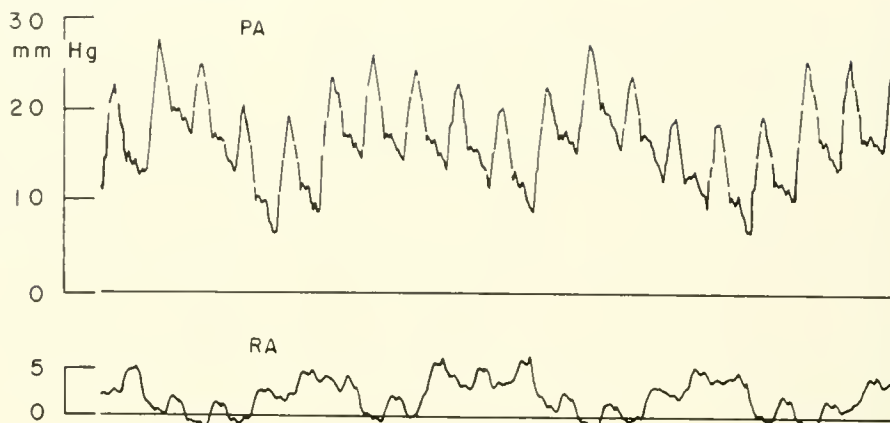
However, there are experimental results which do not fit this picture: *a*) under some circumstances, inspiration has been found to increase—rather than to decrease—pulmonary vascular resistance (49, 115, 309); *b*) measurements of transmural atrial pressures suggest that the pulmonary veins empty uninterruptedly during inspiration (187); and *c*) experiments on models and dogs indicate, that, under circumstances which promote an unusual emptying of the extrathoracic veins, the veins may collapse during inspiration as they enter the thorax, thereby preventing an increase in venous return (308).

At least part of the divergent opinions about the effects of inspiration on the pulmonary circulation seem to arise from failure to take full cognizance of the experimental setting: during an ordinary quiet breath, pulmonary blood flow and volume do appear to increase; if resistance does change, the change is small (354). Moreover, collapse of extrathoracic veins is not apt to occur under ordinary physiological circumstances even though it may conceivably occur in the resting subject who is breathing with enormous tidal volumes (354).

As long as fluctuations in intrathoracic pressure are small and venous return to the right heart remains ample throughout the respiratory cycle, the pulmonary arterial pressure pulses are fairly uniform. However, in clinical conditions associated with low systemic venous return, in chronic pulmonary disease (fig. 38), during exercise and during voluntary deep breathing, marked swings do occur in the pulmonary arterial pressure pulses. These reflect not only the swings in intrathoracic pressure but also changes in blood flow, volume, and resistance (187, 253).

During natural expiration, the filling of the right heart is decreased as intrathoracic pressures approach, or even exceed, caval pressures; the pattern described for inspiration is reversed. In patients with pulmonary disease, in whom expiration has become an active

FIG. 38. Blood pressures recorded from the pulmonary artery (PA) and right atrium (RA) during quiet breathing in a patient with chronic bronchitis and emphysema.



process, venous return to the thorax may become obstructed as positive intrathoracic pressures are imposed on central venous pressures. However, until the systemic venous valves (in the external jugular, subclavian, axillary, and femoral veins) become incompetent from central venous congestion, the rise in central venous pressure is not transmitted to the peripheral systemic veins. Therefore, during a forced expiration, peripheral venous pressure rises only gradually, representing the gradual filling of a distensible system which is obstructed at its thoracic venous outlet.

Inflation of the Lungs

In 1871, Quincke and Pfeiffer reported that positive (intrapulmonary) inflation of the lungs decreases the pulmonary blood volume and increases the resistance to flow (324). Since then, physiologists have debated—on the basis of a wide variety of experiments, models, animal preparations, and intact animals—whether resistance to perfusion increases as the lungs are inflated and if positive pressure inflation exerts the same effects as negative (pleural) pressure inflation (39, 431). It now seems that the discordant results were to be expected because of the nature of the experiments and of the models (62). The principal bases for disagreement seem to have been: *a*) the uncertain meaning of the model under study (354); *b*) the failure to distinguish between transmural pressure and luminal pressure in determining vascular calibers (61); *c*) the mechanical increase in resistance at exceedingly low lung volumes, possibly due to kinking or collapse of small vessels (61); *d*) the mechanical increase in resistance at high degrees of pulmonary distension as resistance vessels are stretched (354); *e*) the influence of the pressure-volume behavior of the lung, and of its enclosed pulmonary vasculature, on the resistance

of the pulmonary vascular bed (397); *f*) the balance of alveolar, pleural, left atrial, and pulmonary arterial pressures which is required to make calculated changes in resistance meaningful (354); and *g*) the probable insignificance of alveolar surface tension in determining pulmonary vascular resistance during either positive (intrapulmonary) or negative (pleural) pressure inflation of the lungs (398). This list also serves to emphasize the fallibility of extrapolating from artificial inflation of the lung to spontaneous breathing.

Positive Pressure Breathing

In the isolated lung, or in the open-chest animal, inflation of the lung from the collapsed position is associated with an initial decrease in resistance as the lung is moderately inflated, followed by an increase in resistance as the lung is distended further (62). Such U-shaped curves have been taken to represent: *a*) a decrease in resistance to blood flow as vessels in the collapsed lungs are unkinked and opened (62), followed by *b*) an increase in resistance due to both a decrease in transmural distending pressure as alveolar pressures increase (191, 215) and mechanical distortion of the resistance vessels at the high lung volumes (215, 397).

In the closed-chest animal, positive pressure breathing affects the pulmonary circulation by increasing alveolar pressure and impeding systemic venous return to the lungs: the systemic venous-right atrial pressure gradient is decreased, thereby decreasing the filling of the right ventricle and right ventricular output (87, 253); the volume of the heart and pulmonary vessels decreases. As a result of the combination of a decreased right ventricular output and a sustained left ventricular output, the pulmonary blood volume

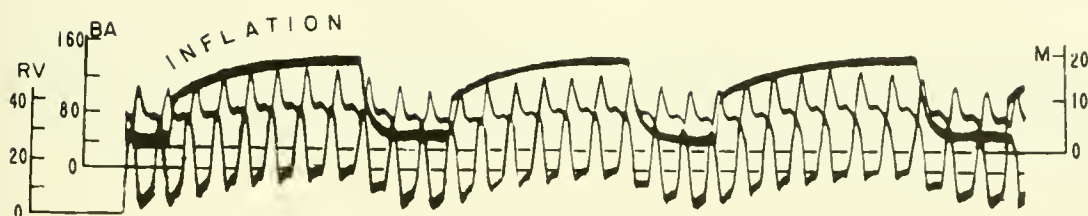


FIG. 39. Schematic representation of the influence of positive pressure breathing on the right ventricular (RV) and systemic arterial (BA) pressures of a normal human subject. The mask pressure (M) appears above the pressure pulses. All pressures are in mm Hg. During inflation, as mask (and pleural) pressures increase, the pulse pressure in the right ventricle progressively decreases; concomitantly, the systemic arterial pulse pressure increases. During expiration, the reverse occurs. The prompt return of the mask pressure to ambient pressure accounts for the ability of expiration to compensate for the inspiratory deficit in blood flow. [After Richards *et al.* (340).]

decreases (395) and the pulmonary vascular resistance increases (49). Although the imposed pressure raises pulmonary vascular luminal pressures the transmural pressures are virtually unaffected (253), and the pressure gradient along the length of the pulmonary vascular tree remains essentially unchanged (187, 256). The circulatory changes arising from the imposed pressure reverse promptly once the lungs are vented to atmosphere (fig. 39).

In systemic hypotensive states, positive pressure breathing may precipitate circulatory collapse if compensatory mechanisms are insufficient to sustain the venous return to the right heart (49). Not only are the output of the right heart and the pulmonary blood volume reduced, but the normal balance between alveolar perfusion and alveolar ventilation is also upset so that portions of the lung become excessively ventilated with respect to perfusion (160).

A variety of mechanical devices are in common use for intermittent positive pressure breathing (426). Their effects on the circulation are functions of the degree and duration of the cyclic swings which they induce in intrathoracic pressure. The cardiac output generally falls (11) in proportion to the mean increase in intrathoracic pressure; in practice, the cardiac output may be kept at control levels by using cycling devices which operate to: *a*) inflate the lungs gradually to peak pressure; *b*) decompress the lungs suddenly by venting them to atmosphere; and *c*) allow a longer period of exposure to atmospheric pressure than to positive pressure.

Negative Pressure Breathing (Pleural)

As pressure around the collapsed isolated lung is artificially decreased, its resistance to perfusion decreases (61, 354). The changes in resistance which accompany further inflation of this type are unsettled.

Thus, some have found only a continuing decrease in resistance as the lung is expanded by progressive decrements in "pleural pressure" (62); others have found U-shaped curves in which the initial drop in resistance as the lung begins to expand (pleural pressure -5 to -10 cm H₂O) is succeeded by an increase in resistance as the pleural pressure decreases further (pleural pressure -10 to -25 cm H₂O) (354, 397). The nadir in resistance occurs at half-maximal lung volume.

The mechanisms proposed to account for these divergent results are enlightening. The initial decrease in resistance—to which all agree—has been attributed to either an increase in transmural pressure or to the unkinking of "gnarly" vessels (61). Different explanations have been used to account for the divergent results at high levels of inflation: those who find a continued drop in resistance ascribe it to the continued increase in transmural pressure as "pleural" pressure drops (62); those who find that resistance finally increases believe that at lung volumes exceeding 50 per cent of maximal, mechanical distortion of the pulmonary vessels—a function of lung volume rather than of transmural pressure—is involved (354, 397). While these studies leave unsettled the question of the behavior of the pulmonary vascular resistance as the lung is progressively inflated, they do serve as a reminder that the transmural pressures, which account satisfactorily for passive changes in caliber at moderate degrees of inflation, may be supplanted by other mechanical influences, e.g., stretching or collapse, in determining vascular calibers at extreme inflation or deflation.

Negative Pressure Breathing (Intrapulmonary)

"Snorkel" breathing is characterized by a lower pressure within the lungs than around the body (49).

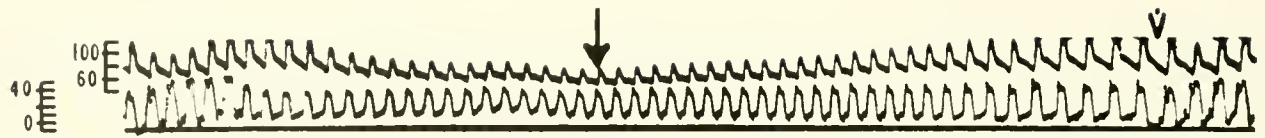


FIG. 40. Effects of a prolonged forced expiration on systemic arterial pressures (*upper tracing*) and right ventricular (*lower tracing*) pressures in a patient with chronic pulmonary emphysema and fibrosis. Ten seconds after the start of expiration (solid arrow), the amplitude of the RV pressure pulse begins to increase, after several beats, there is a progressive rise in the femoral arterial systolic, diastolic, and pulse pressures. This suggests that as the flow of blood into the thorax is impeded, the volume of the peripheral venous reservoir slowly increases until the venous pressure becomes sufficiently great again to increase the right heart filling and output, in spite of the continued elevation of the intrathoracic pressure. During the succeeding inspiration (hollow arrow), a further augmentation of the right ventricular pulse pressure occurs (last four beats). [After Lauson, *et al.* (253).]

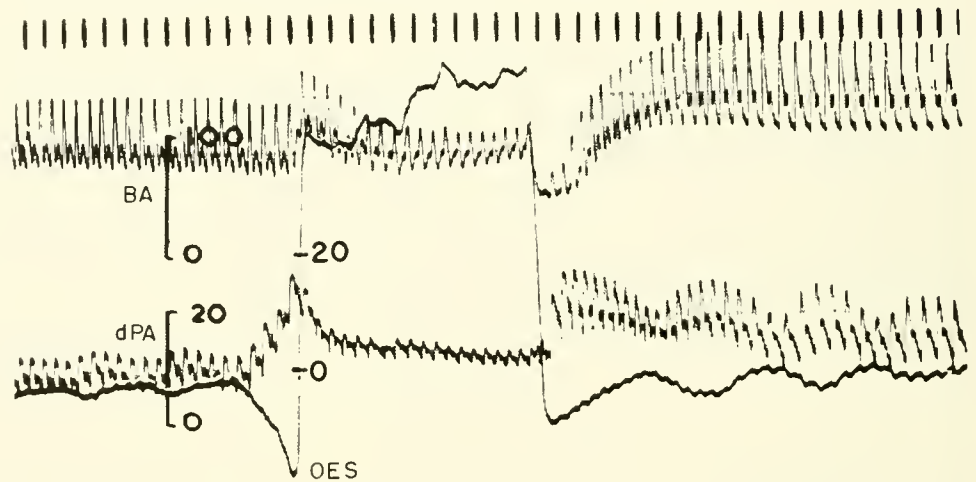


FIG. 41. Effect of the Valsalva maneuver on brachial arterial pressure (BA) and "transmural" pulmonary arterial pressure (dPA). The changes in intrathoracic pressure, measured as the esophageal pressure (OES), indicate the onset, duration, and end of the expiratory effort. All pressures are in mm Hg. The overshoot in the systemic arterial response following the Valsalva maneuver is ascribed to reflex vasoconstriction. On the other hand, the pattern of change in pulmonary arterial pressure is attributed to mechanical events, i.e., to alterations in venous return and right ventricular output. [After Lee *et al.* (255).]

At the start of negative (intrapulmonary) pressure breathing the systemic venous return to the lungs and the pulmonary blood volume increase (49). In contrast to positive pressure breathing, the negative intrapulmonary pressures distend the intrapulmonary vessels (256). At the small lung volumes, associated with continuous negative pressure breathing, atelectasis may develop.

Cough

During a cough, pressure referred to atmosphere rises simultaneously and equally in the thorax (fig. 21), abdomen, and cerebrospinal canal (190). The increase in pressure (which may transiently reach

levels of 150 mm Hg) does not strain the intrathoracic (255) or abdominal or cerebrospinal vessels, and does not, per se, affect the pressure gradient which drives blood along the pulmonary vascular tree. However, it is propagated to the peripheral arterial tree where it causes a marked increase in the transmural distending pressure (190).

Prolonged Expiration

During a prolonged expiration (fig. 40), the amplitude of the pulmonary arterial (and right ventricular) pressure pulse first decreases and then gradually increases; the systemic arterial blood pressures undergo a similar pattern of change. This sequence has been

interpreted as reflecting the gradual increase in peripheral venous blood volume and pressure during the sustained expiration until adequate filling of the right, and then the left, heart is restored (187, 253).

Forced Expiration (Valsalva)

The effects of the Valsalva maneuver (forced expiration against a closed glottis or a column of water 30 to 40 cm high) (fig. 41), has been more intensively studied in the systemic circulation than in the pulmonary circulation (255). Shortly after the start of the maneuver, the distending pulmonary arterial pressure falls abruptly as the filling pressure of the heart is reduced by the increased intrathoracic pressure (187, 253); it remains low during the period of strain. Upon release of the expiratory effort, pulmonary arterial mean and pulse pressures "overshoot" the prestrain level, but to a lesser extent than in the systemic arteries. During the maneuver, considerable quantities of blood may be displaced from the thorax to the periphery (253). The systemic arterial overshoot seems to involve a combination of an increased cardiac output and vasoconstriction; although some believe that these same mechanisms are involved in the pulmonary arterial overshoot, the evidence for pulmonary vasoconstriction is much more tenuous than for systemic vasoconstriction (255).

OCCLUSION OF A PULMONARY ARTERY

In principle, occlusion of larger and larger portions of the pulmonary arterial tree provides a simple tool



FIG. 42. Effect of complete occlusion of one pulmonary artery on ipsilateral oxygen uptake. Before inflation of the occlusive balloon in the right pulmonary artery (*left panel*), both lungs share almost equally in the oxygen uptake. The *middle panel* shows the occlusive balloon, inflated with Diodrast, positioned at the end of a cardiac catheter in the right pulmonary artery. After complete occlusion, the oxygen uptake by the right lung ceases. [After Fishman *et al.* (139).]

for testing the passive effects of an increase in pulmonary blood flow on pulmonary arterial pressures (fig. 34) and pulmonary vascular resistance. In the open-chest dog, graded occlusion of the pulmonary vascular tree is easily performed (194). The situation is much more complicated in the closed-chest dog or man in whom balloon-tipped, venous catheters are guided, under fluoroscopic control, into a pulmonary artery; in this experimental situation additional techniques, such as bronchspirometry, are required to establish the degree of occlusion which has been accomplished (fig. 42).

In wondrous contrast to the catastrophic effects occluding the pulmonary vascular tree by emboli, inflation of a balloon in one pulmonary artery is entirely innocuous: the metabolic rate, the total cardiac output, the systemic arterial and left atrial blood pressures, and the heart rate remain unchanged; the total ventilation rarely increases by more than 10 per cent (53, 101). However, even this slight change in total minute ventilation helps to adapt the alveolar ventilation to the altered pulmonary capillary perfusion (390).

The first studies of the pulmonary circulation following occlusion of one pulmonary artery were made in 1876 on the open-chest dog (132). These indicated that the pulmonary arterial pressure, measured proximal to the site of occlusion, increased by 50 per cent following interruption of the blood flow to one lung. Subsequently, a similar procedure in other open-chest animals found lesser increases, ranging from zero in the rabbit (125) to 20 per cent in the cat (125). More puzzling than these divergent results in the different species is the fact that in the intact dog, occlusion of one pulmonary artery by a balloon-tipped catheter has also produced variable effects: on the one hand are results indicating that pulmonary arterial pressure remains essentially unchanged (68, 101); other results indicate an increase in pressure of the order of 33 per cent (252, 259). However, since none of the experiments in the dog verified the degree of pulmonary arterial occlusion produced by the inflated balloon, it seems reasonable to assume that inflation of the balloon was not equally successful in producing complete occlusion in the different dogs, and that the larger increments in pulmonary arterial pressure—i.e., of the order of 33 per cent (252, 259)—represent the more complete occlusions.

In man the results have been more consistent: after complete occlusion of one pulmonary artery, the pulmonary arterial pressure (primarily systolic) proximal to the occlusion increases, the pulmonary

blood volume on the patent side also increases, the pulmonary circulation time decreases and the pulmonary vascular resistance decreases (42, 101). Because of the configuration of the trachea in the dog, the completeness of the unilateral interruption of blood flow is more readily checked by bronchospirrometry in man (fig. 42); when the right ventricular output has been shown to be completely diverted to one lung in man, the pulmonary arterial pressure has been found to increase by 30 to 40 per cent (5 to 7 mm Hg), and the calculated resistance to fall to 40 or 50 per cent of the initial value (42, 53, 101). The increase in pulmonary arterial pressure seems entirely attributable to the passive consequences of an augmented pulmonary blood flow and volume.

EFFECTS OF EXERCISE ON PULMONARY CIRCULATION

Exercise is a practical expedient for increasing pulmonary blood flow. However, by comparison with unilateral occlusion of one pulmonary artery, it suffers the disadvantage of simultaneously evoking changes in the ventilation, in the performance of the heart, and in a variety of circulatory parameters.

Experimentally, dog and man have been exercised in various different ways: electrical stimulation, ergometer, push-pedal, and treadmill. The workload imposed by the exercise, as well as the efficiency with which the exercise is performed, varies with the type of exercise, the position in which it is performed, and the familiarity with the exercise (7, 12). For practical reasons, the work load is generally inferred from the increase in oxygen uptake rather than measured directly (216).

Pulmonary Blood Flow

The first measurements of the cardiac output during exercise were made by foreign gas methods (240). Since then, with few exceptions (3), the foreign gas methods have been superseded by indicator-dilution methods and by applications of the Fick principle.

For accuracy, the use of the Fick method during exercise requires that the oxygen uptake at the mouth provide a precise measure of the oxygen uptake by pulmonary capillary blood, and that the pulmonary arteriovenous oxygen difference be constant. These criteria are most apt to be satisfied when respiration and circulation become stable, i.e., when minute ventilation, respiratory exchange ratio, oxygen up-

take, heart rate, arteriovenous oxygen difference, and cardiac output no longer vary with time. Unfortunately, all these parameters do not stabilize simultaneously (108, 109, 136). Thus, the oxygen uptake at the mouth, and the arteriovenous oxygen difference may level off after 1 min of heavy exercise (up to 1200 ml min⁻¹ m²), whereas the respiratory exchange ratio and the ventilation require much longer to reach a plateau. As long as the respiratory gas exchange is unstable, it is difficult to be sure that the measurement of the oxygen uptake at the mouth provides a reliable value for the numerator of the Fick equation, i.e., of the oxygen taken up by blood perfusing the pulmonary capillaries. On the other hand, when both the respiration and circulation become stable—usually within 3 min in normal subjects performing light, supine exercise (O₂ uptake up to 400 ml min⁻¹ m²)—the prospect of an accurate measurement of pulmonary blood flow is increased (212). Obviously, during heavy exercise (O₂ uptake greater than 1000 ml min⁻¹ m²), it may become difficult to achieve a steady state; indeed, as exhaustion is approached, the Fick method may become completely unreliable. It is apparent that these considerations do not support the practice of applying the Fick principle to the measurement of the cardiac output during brief periods of heavy exercise (108, 109). It would be reassuring if this use of the Fick principle were validated by another independent method, such as the Stewart-Hamilton, which, in principle, requires a briefer steady state.

Blood Flow and Oxygen Uptake

In the unanesthetized dog (12) and in normal man (104, 149, 335), an increment in oxygen uptake ($\Delta\dot{V}_{O_2}$) of 100 ml is usually associated with an increment in cardiac output ($\Delta\dot{Q}$) of 600 to 800 ml. However, both lower (101, 109, 258) and higher (101) ratios of $\Delta\dot{Q}/\Delta\dot{V}_{O_2}$ have also been observed. One likely explanation for at least part of the variability is that different degrees of approach to the "basal" state were achieved prior to exercise in the different studies: it has been shown that in those studies in which a serious attempt is made to achieve a basal pre-exercise state, the ratio $\Delta\dot{Q}/\Delta\dot{V}_{O_2}$ may even exceed 1 liter of cardiac output per 100 ml of oxygen uptake (132); conversely, when a nonbasal state exists prior to the exercise, the ratio $\Delta\dot{Q}/\Delta\dot{V}_{O_2}$ may fall below 600 ml (109). This point is emphasized by the solid line of figure 12, which indicates that for a given level of oxygen uptake the cardiac output during excitement is higher than

during exercise; this effect may continue, to an unpredictable degree, during mild exercise.

In heart failure the ratio $\Delta\dot{Q}:\Delta\dot{V}_{O_2}$ is often abnormally low, i.e., less than 600 ml increase in flow per 100 ml increase in oxygen uptake. A striking dissociation between $\Delta\dot{Q}$ and $\Delta\dot{V}_{O_2}$ follows the exhibition of dinitrophenol, so that the cardiac output continues at basal levels even though oxygen uptake increases tremendously (216).

Arteriovenous Oxygen Difference

The pulmonary arteriovenous oxygen difference increases during exercise. However, in contrast to the roughly linear relation between cardiac output and oxygen uptake during graded exercise, the relation between the arteriovenous oxygen difference and oxygen consumption is clearly hyperbolic (109, 382). Whether the oxygen requirements of the tissue are met predominantly by an increase in cardiac output or by a greater extraction of oxygen from each unit of blood perfusing the tissues seems to depend, at least in part, on the type of exercise, the body position in which the exercise is performed, and the ambient temperature (7, 336). Parenthetically, it is of interest that during graded exercise (up to 2000 ml min/m²) trained and untrained subjects increase cardiac output and widen arteriovenous differences for oxygen in an identical fashion (149).

Pulmonary Vascular Pressures

Because of the difficulty in measuring intrathoracic pressures, pulmonary vascular pressures are conventionally referred to atmosphere. In only one study were they also referred to esophageal pressures (109); this study suggested that conventional luminal pressures tend to underestimate slightly the transmural pressures. Before considering the change in pulmonary artery pressure during exercise, it is relevant to recall that: *a*) pulmonary vascular pressures are difficult to measure accurately during exercise since respiratory swings are marked and the records are apt to be distorted by artifacts, and *b*) especially during severe exercise, shifts in mid-position of the lung and changes in compliance confuse the recognition of the mechanisms involved in a change in pressure (109).

Until a few years ago, because of the practical difficulties in measuring small changes in pressure during exercise, it was uncertain if light (supine) exercise elicited an increase in pulmonary arterial

pressure (104, 208, 346). Indeed, an appreciable increase was believed to occur only at levels of exercise which tripled the cardiac output (89). However, recent refinements in manometric methods, coupled with the substitution of continuous pressure recording for the tedious process of measuring and integrating individual pressure pulses, have established that the pulmonary arterial pressure increases (by 3–5 mm Hg) even during light supine exercise (132, 370, 383).

The behavior of the pulmonary arterial pressure during light exercise is quite stereotyped (fig. 28): at the start of the exercise, the (luminal) pulmonary arterial pressure increases abruptly by 3 to 5 mm Hg. As exercise is continued, a plateau is reached, generally 1 to 2 mm Hg less than peak values (132, 382). The increase in systolic pressure exceeds the increase in diastolic pressure. As a rule, the higher the pre-exercise level of the pulmonary arterial pressures, the higher the values reached during exercise. Immediately after the exercise, the pulmonary arterial pressure often falls below control, resting values (109, 132, 382).

The pulmonary arterial flow-pressure points obtained by different investigators during graded exercise are superimposed on the pressure-flow line of figure 34. At the lower grades of exercise, the points fall along the flow-pressure curve obtained in the course of progressive curtailment of the pulmonary vascular bed by balloon-occlusion. At the higher grades of exercise the pulmonary arterial pressure at any given level of blood flow tends to exceed the corresponding pressure during balloon-occlusion.

Direct measurements of the left atrial pressure during exercise in intact man or dog have not been reported. On the other hand, in dogs exercised by electrical stimulation of the extremities, the left atrial pressure remains unchanged (125); unfortunately, the level of exercise in these experiments is unknown. In man the slight increments of the pulmonary arterial pressure during mild exercise suggest that if the left atrial pressure does increase, the increase cannot exceed a few mm Hg. The pulmonary "wedge" pressure is unaffected by mild exercise but may increase slightly during severer exercise (104).

Pulmonary Blood Volume

There is considerable indirect evidence to indicate that the pulmonary blood volume increases during supine exercise: the central blood volume increases (48, 101), the pulmonary compliance decreases (279), and, except for the muscles (250), the regional blood

volume decrease (48). However, such evidence applies only to the steady part of the exercise; more difficult to ascertain is the pattern of change in the pulmonary blood volume from the start to the finish of the exercise. In this regard, the most convincing clue is the characteristic sequence of changes in the pulmonary arterial pressure (fig. 28); this pattern is consistent with an abrupt increase in the pulmonary blood volume at the start of the supine exercise, a gradual stabilization at below-peak values as exercise is continued, and a prompt fall to below resting values when exercise is arrested (109, 132). How the increased blood volume is apportioned among the different vascular segments of the lung is unknown; however, the pulmonary capillaries apparently share in the increase (364).

Pulmonary Vascular Resistance

The calculated pulmonary vascular resistance either remains unaltered (109) or, more often, decreases (101, 346) during light to moderate (supine) exercise. Although it is generally believed that the decrease in calculated resistance at these levels of exercise represents both the widening of patent pulmonary vessels and the opening of closed vessels (208, 241, 346), the particular mechanisms which are responsible for this change in vascular geometry remain speculative. Three reasonable alternatives come to mind: active pulmonary vasodilatation, passive dilatation by the decrease in pleural pressure, or passive dilatation by the increase in luminal pulmonary arterial blood pressure. Of the three alternatives, the passive increase in pulmonary arterial luminal (and transmural) pressure seems sufficient—without invoking vasomotricity—to account for the widening and opening of the pulmonary vessels at these low grades of exercise (187).

During heavy exercise, as the pulmonary blood flow is more than tripled, the pulmonary vascular resistance (calculated on the basis of an assumed left atrial pressure) is described as becoming constant (252). As pointed out previously, the pulmonary vascular tree is then pictured as behaving as though it were comprised of "rigid tubes"; the "rigid tubes," in turn, are envisaged as wide-open, low-resistance vessels with elastic fibers stretched to tighten their collagen "jackets" (187). Generally speaking, the calculations of pulmonary vascular resistance during heavy exercise on the basis of pulmonary arterial pressure and flow (fig. 34) are consistent with this view. However, this interpretation of calculated resistance is handicapped by the lack of assurance

concerning the simultaneous behavior of the left atrial pressure, the pulmonary blood volume and the pleural pressures. Indeed, without information about these critical parameters, the ratio of pulmonary arterial pressure to pulmonary blood flow during heavy exercise may represent either an increase or a decrease in pulmonary vascular resistance. Finally, as indicated previously, not only may the kinetic energy in the pulmonary artery exceed the potential energy at high rates of pulmonary blood flow, but interconversions of potential and kinetic energy are bound to occur along the length of the pulmonary vascular tree (20). Consequently, during heavy exercise, even the ratio of the pulmonary vascular pressure gradient (potential energy gradient) to the pulmonary blood flow need not provide a reliable index of pulmonary vascular dimensions.

MISCELLANEOUS MECHANICAL INFLUENCES

Heart Rate

In normal dog and man, speeding up of the heart rate by atropine, is ordinarily without appreciable effect on pulmonary vascular blood pressures or blood flow (424); in some instances the cardiac output may increase by 40 to 50 per cent (168). In patients with "tight" mitral stenosis, even the slight increment in cardiac output induced by atropine may suffice to precipitate pulmonary edema by elevating pulmonary venous and pulmonary capillary pressures.

Slowing of the heart has been produced by vagal stimulation in dogs: as the heart rate drops to one-half or one-third of the initial value, the cardiac output falls and the pulmonary venous pressure rises (65). A similar combination of bradycardia, low cardiac output, and high pulmonary venous pressure also occurs when intracranial pressure is considerably increased; in this case, the occurrence of pulmonary edema is often potentiated by left ventricular failure from intense systemic vasoconstriction. Measures which prevent the bradycardia or left ventricular overwork also protect against the pulmonary edema of increased intracranial pressure (65).

"Bronchomotor Tone"

This colloquialism refers to a state of partial contraction of bronchial smooth muscle (95, 132, 351). An increase in "bronchomotor tone" may conceivably affect pulmonary vascular dimensions in at least three

different ways: 1) by mechanical distortion of the pulmonary arterial tree and of the large pulmonary veins which lie adjacent to the tracheobronchial tree; 2) by raising intra-alveolar pressure to compress the pulmonary capillaries and to increase, thereby, their resistance to perfusion; and 3) by increasing the "elastance" of the lung (19, 305, 351), i.e., the elastic forces which are developed during each respiratory cycle. Many experimental (95, 305) and clinical observations attest to the capacity of the bronchial smooth muscle to undergo drastic changes in tone in response to appropriate stimulation; this severe type of bronchospasm poses no problem in recognition. More troublesome is the prospect that subtle changes in "bronchomotor tone" may escape detection (351). As a general approach, bronchomotor tone may reasonably be considered to remain unchanged during the course of an experiment if: *a*) clinical evidences of bronchial obstruction or dyspnea do not appear; *b*) the ventilatory pattern remains unchanged; and *c*) the mechanical properties of the lungs remain unaltered (132, 153). When the nature of the experiment precludes such clinical and experimental stability, decision as to the influence of altered bronchomotor tone on pulmonary hemodynamics falls to the experimenter.

Mechanical Compression (Atelectasis)

It is well known that mechanical factors influence the caliber of the pulmonary blood vessels and their resistance to blood flow. For example, at a given hydrostatic pressure head, moderately inflated lungs contain more blood (wider vascular calibers) than do either collapsed or markedly distended lungs (146); similarly, pneumothorax not only decreases the air content of the lungs but also shrinks the vascular calibers (380).

Atelectasis is generally believed to affect the pulmonary circulation by mechanical compression. It has been produced experimentally by bronchial obstruction (85, 94), pneumothorax (380) and sustained hypoventilation (359). The changes following bronchial obstruction have been most intensively studied: following complete occlusion of a bronchus, gas is absorbed at a rate set by the composition of the gas, the surface area and the rate of perfusion of the affected area (94). As the gas content of the lung decreases, the mechanical compression of the pulmonary blood vessels—particularly of the capillaries in the collapsed alveoli—diverts the blood flow from the atelectatic to the unaffected parts of the lung (85, 380).

Following complete collapse, only 10 to 15 per cent of the cardiac output perfuses the collapsed lung (316).

Several different ways have been used to trace the sequential changes in perfusion following bronchial obstruction: the change in peripheral arterial oxygenation (316), the change in "venous admixture" (23) and angiography (85). Although not entirely consistent (5), the results seem to indicate that within an hour after the bronchial obstruction, the blood flow to the nonventilating lung is apt to decrease by 30 to 40 per cent (316). In time, the blood flow to the nonventilating lung decreases further; up to a month may be required for nearly all mixed venous blood to be excluded from the atelectatic lung and for systemic arterial oxygenation to return toward normal values (85). By way of contrast, the spontaneous restoration of systemic arterial oxygenation in patients with pneumonia or pneumothorax is more often a matter of days than of weeks.

The observation has been made that the pulmonary collateral circulation may proliferate in atelectatic areas. However, the strong possibility exists that complications of atelectasis, such as pulmonary infection, rather than the mechanical collapse, per se, are responsible for the expanded collateral circulation (316).

Hypertonic Solutions

A particularly puzzling phenomenon has been the occurrence of pulmonary arterial hypertension following the injection of hyperosmotic solutions, e.g., 20 per cent sodium chloride, into a peripheral vein (28). Different mechanisms have been proposed to account for this pressor response, including selective constriction of the superior pulmonary veins at their entry into the left atrium (120). Recently, microscopic examination has shown that intravascular red-cell agglutination occurs after the injection of highly concentrated salt and sugar solutions, raising the possibility that luminal obstruction, rather than vasoconstriction, may underlie the pulmonary pressor response to hypertonic solutions (333, 376).

PULMONARY VASOMOTOR ACTIVITY

It has been shown in a previous section that the pulmonary circulation is equipped with vascular smooth muscle and nerves, and that the pulmonary circulation has the ability to vasoconstrict and to vasodilate. Much more difficult to decide is whether

this capacity for vasoconstriction is actually used by the intact animal under natural conditions: the strength of such a decision depends on the degree to which all conceivable passive influences on the pulmonary circulation have to be appraised and found wanting. And the list of potential passive influences is apt to be longer for experiments performed under natural conditions than under contrived experimental conditions (387).

Recognizing that final proof of the operation of pulmonary vasomotor activity under natural conditions is difficult to obtain, there is, nonetheless, reasonable evidence to indicate that it does occur; this evidence is of two types: 1) the response of the pulmonary circulation to acute hypoxia and to acute acidosis and 2) the occurrence of pulmonary vasomotor reflex activity. More uncertain is the occurrence of pulmonary vasomotor waves.

Respiratory Gases

The first experiments devoted to the effects of the respiratory gases on the pulmonary circulation were concerned with asphyxia. Although these experiments did show that asphyxia elicited pulmonary hypertension, they made no attempt to distinguish which of the respiratory gases was responsible for the rise in pressure. Thirty years later, acute hypoxia, per se, was shown to be capable of eliciting pulmonary hypertension in the anesthetized dog (132). Thereafter, interest in the respiratory gases was episodic until 1946, when Euler and Liljestrand demonstrated that acute hypoxia and acute hypercapnia evoked an increase in pulmonary arterial pressure in the anesthetized cat and that this pressor response occurred in the face of an unchanged or a decreased left atrial pressure (125, 268). Although these experiments were inconclusive in some respects—e.g., the lack of meas-

urement of pulmonary blood flow or peripheral arterial oxygen saturation or pH—they constituted a landmark in the study of the pulmonary circulation because of the clairvoyant hypothesis which they suggested and the subsequent work which they stimulated. The hypothesis consisted of three parts: 1) that a change in the composition of the inspired gas is capable of eliciting an increase in resistance and that this increase in resistance stems, in turn, from pulmonary vasoconstriction; 2) that this vasoconstriction is mediated by local vasomotor responses rather than by reflexes involving the extrapulmonary portions of the autonomic nervous system; and 3) that the vasomotor effects of the respiratory gases serve to adjust alveolar perfusion to alveolar ventilation. Subsequent experiences have done more to supply and clarify details than to alter the general structure of the hypothesis; in particular, they have distinguished between the effects of acute hypoxia, acute hypercapnia, and respiratory acidosis on the pulmonary circulation.

Acute Hypoxia

A reduction in the fraction of oxygen in the inspired air—generally below 12 per cent—has elicited an increase in pulmonary arterial pressure in every species in which it has been tested (132). In the intact, unanesthetized animal and man this pressor response generally occurs when the oxygen saturation of peripheral arterial blood drops below 80 per cent (136). The associated increase in mean pressure is of the order of 4 to 8 mm Hg (fig. 43) (300). Only a small part of this increase in pressure is attributable to an increase in pulmonary blood flow: during the breathing of a 10 per cent oxygen mixture the increase in flow rarely exceeds 30 per cent (132). Since the usual passive determinants of pulmonary vascular pressure—pulmonary blood volume (154), ventila-

FIG. 43. Effect of acute hypoxia on pulmonary arterial pressure. During acute hypoxia, the systolic, diastolic, and mean blood pressures increase. The heart rate also increases and respiratory fluctuations in the luminal pressures (referred to atmosphere) become more marked.

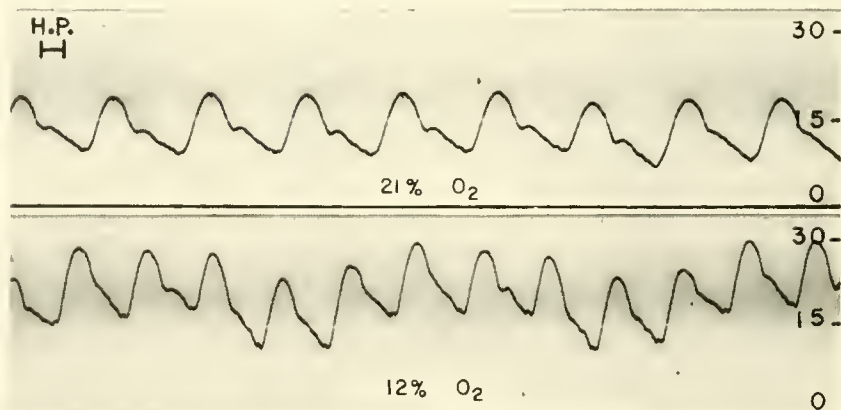


TABLE 3. *Representative Oxygen Tensions of Precapillary and Postcapillary Pulmonary Vessels During Various Experimental Circumstances*

| | Mixed Venous P_{O_2} mm Hg | Pulmonary Venous P_{O_2} mm Hg |
|--------------------------------|---------------------------------|-------------------------------------|
| Rest; ambient air | 40 | 100 |
| Moderate exercise; ambient air | 30 | 105 |
| Bilateral hypoxia; 12% O_2 | 30 | 45 |
| Unilateral hypoxia; 5% O_2 | 35 | 35* |

* Pulmonary venous P_{O_2} on the opposite side, i.e., the hyperoxic side, exceeds 100 mm Hg.

tion (132), and left atrial pressure (125, 303)—undergo too little change to affect the level of pulmonary arterial pressure, the increase in the blood pressure gradient across the lungs is generally acknowledged to involve an active increase in pulmonary vascular resistance, i.e., vasoconstriction.

In essence, the evidence for vasoconstriction during acute hypoxia falls into three categories (132): 1) the disproportionate increase in the pressure gradient across the lung with respect to the increment in pulmonary blood flow (fig. 32) (132); 2) the redistribution of the pulmonary blood flow in favor of the high-oxygen lung during unilateral hypoxia (209, 328, 408); and 3) the vasodilator effects of infused acetylcholine during bilateral (153) and unilateral (90) hypoxia. Despite this cumulative evidence, not all are convinced that acute hypoxia elicits pulmonary vasoconstriction (353). However, although the evidence against pulmonary vasoconstriction is not very substantial, it does serve to recall: *a*) that the magnitude of the changes in pulmonary vascular blood pressure is small; *b*) the possibility that subtle extraneous influences, such as constriction of the extravascular smooth muscle may mimic vasoconstriction; and *c*) that the effects of acute hypoxia on the pulmonary circulation are easily overwhelmed by known mechanical influences, such as gravity (132).

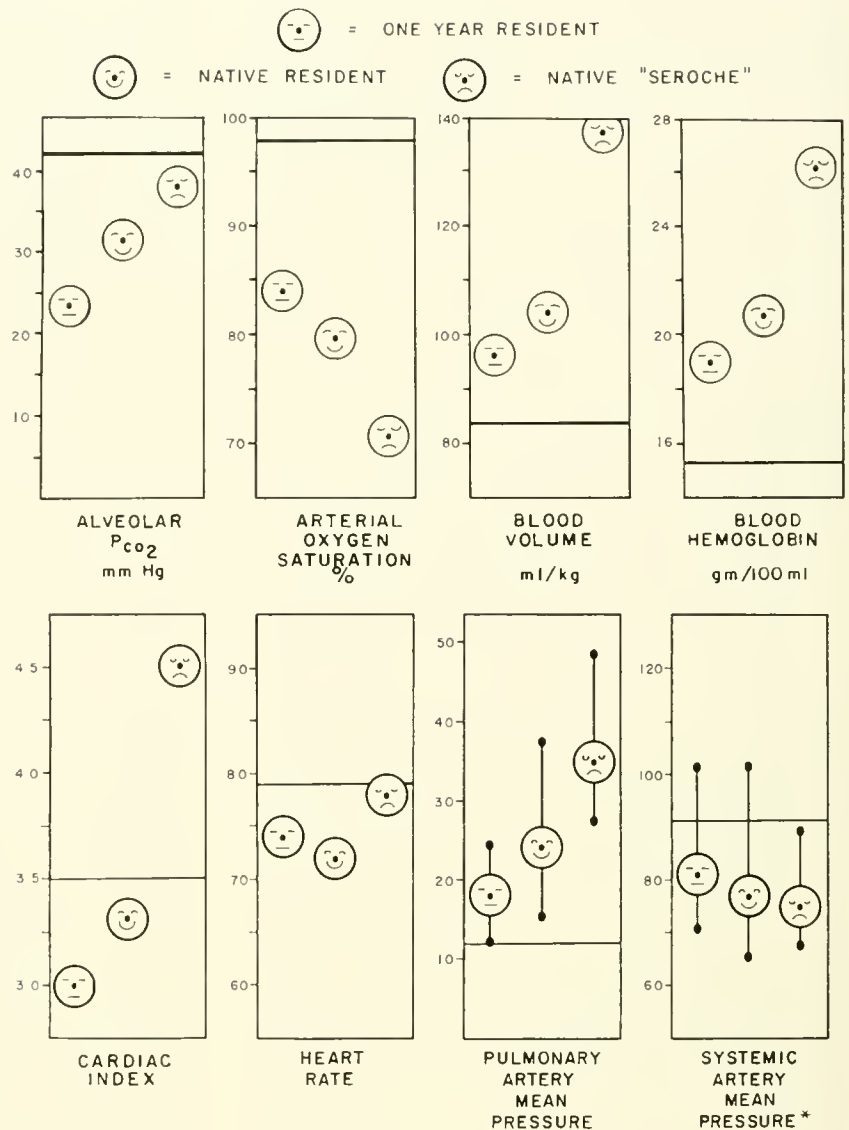
The particular vascular segment, or segments, involved in the pulmonary vasoconstriction has been sought in many ways. At the moment, the experiments performed under exceedingly artificial conditions favor postcapillary vasoconstriction. On the other hand, experiments in intact animals with dinitrophenol (which selectively lowers precapillary oxygen tension) have demonstrated precapillary vasoconstriction (Bergofsky *et al.*, unpublished observations). No evidence has yet been adduced to indicate that pulmonary venous-left atrial junctions constrict during hypoxia. The opinion of the author is that

both the precapillary small vessels and the postcapillary small vessels can constrict if exposed to a sufficient degree of hypoxia (132). An idea of the oxygen tensions which exist in the pre- and postcapillary segments under various conditions is given in table 3.

The notion that the small pulmonary muscular vessels, regardless of location, constrict when exposed to a sufficiently intense hypoxic stimulus implies that during ambient air breathing the hypoxic mixed venous blood may set the tone (albeit slight) of the pulmonary "arterioles" and, thereby, the level of the pulmonary arterial pressure; this tonic effect would presumably be heightened during exercise (as mixed venous blood becomes more unsaturated) unless the arterioles were passively widened by mechanical influences. The experiments involving hypoxia by airway are also complicated. In these, the prospect exists that the hypoxic mixture may affect the precapillary as well as the postcapillary segments; nonetheless, the postcapillary segments would be more drastically affected because mixed venous blood is ordinarily low in oxygen tension. Finally, vasoconstriction of either segment could account for some rearrangement of the pulmonary blood flow in patients with maldistribution of air and blood even though mechanical influences would be expected to be prepotent.

Several other aspects of the pressor response to acute hypoxia warrant special emphasis: *a*) the increase in vascular resistance in the isolated perfused lung—which is devoid of neurohumoral influences, of a collateral circulation, and of extrapulmonary reflexes—indicates that hypoxia acts locally, i.e., either by a direct chemo-effect on the vessel, or by way of an intrapulmonary reflex, rather than by way of extrapulmonary controls (116, 305); *b*) the persistence of the pressor response after ergotamine and atropine favors a direct rather than a reflex action (116, 125); *c*) severe hypoxia or anoxia, as commonly used in the isolated lung or in artificial preparations, may not represent the same biochemical stimulus to vascular smooth muscle as tolerable levels of hypoxia in animal or man (132); *d*) the pulmonary vasoconstriction evoked by hypoxia has to be reconciled with the fact that hypoxia dilates most intact vascular beds, constricts isolated vessels, and dilates the placental vessels (137); *e*) the biochemical mechanism by which acute hypoxia causes smooth muscle to constrict has not been elucidated (116); *f*) the catecholamines are not involved in the pressor response to moderate hypoxia (163); and *g*) the vasoconstriction evoked by

FIG. 44. Schematic representation of respiratory and circulatory measurements of man at altitude (14,900 feet). The horizontal line in each panel represents a typical sea-level value. [Based on Rotta *et al.* (362).]



acute hypoxia is easily overcome by mechanical influences, such as gravity (2).

Chronic Hypoxia

Chronic hypoxia and hypoxemia are regular features of life at high altitudes. At the Fifth Annual Conference on Research in Emphysema, held at Aspen, Colorado, June 15–18, 1962, Peñaloza, Sime, Banchero, and Gamboa enlarged upon the earlier observations of Hurtado and co-workers at Morococha (Peru) (altitude of 14,900 feet, atmospheric oxygen tension of 80 mm Hg) (fig. 44) (362). They confirmed, on the basis of right heart catheterization in 38 native residents of Morococha, that mild pulmo-

nary hypertension (of the order of 41 ± 15, 28 mm Hg) coexisted with normal cardiac output (average of 3.7 l/min/m²) and with normal pulmonary wedge pressure and heart rate. During strenuous supine exercise (four- to fivefold increase in oxygen uptake), the doubling of blood flow (from 3.65 to 7.49 l/min/m²) was associated with a doubling of the pulmonary arterial pressure (from 41 ± 15, 29 to 77 ± 40, 60). In resting subjects, the breathing of 35 per cent oxygen (or the infusion of acetylcholine) reduced the pulmonary arterial pressures somewhat (by 20 to 25 per cent) but not quite to normal sea level values. Restudy of 11 altitude dwellers after two years at sea level disclosed that the blood gases, the respiration, and the circulation had returned to virtually normal sea level

values at rest but that the increment in pulmonary arterial pressure during exercise was still excessive for the increment in blood flow.

Peñaloza *et al.* also found that young children (1–5 years of age), born and raised at altitude, had more marked pulmonary hypertension (of the order of 58/32, 45 mm Hg) than older children (of the order of 41/18, 28 mm Hg) and adults; in this respect, the youngsters at altitude differed strikingly from their counterparts at sea level who achieved normal pulmonary arterial pressures during the third to sixth month of life.

Pulmonary hypertension and right ventricular enlargement are characteristic not only of acclimatized man but also of acclimatized cattle (199). Malacclimatization to altitude results in "mountain sickness," both in man and in animals. Although mountain sickness is not a distinct clinical entity, at least two different types have been identified, i.e., "brisket disease" in cattle and "seroche" in man (table 4); both seem to originate in alveolar hypoventilation. Seroche is manifested by polycythemia, easy fatigability, and respiratory distress during exertion; its physiological hallmarks are severe hypoxemia, hypercapnia, polycythemia, and pulmonary hypertension (9, 362). Removal of the native suffering from seroche to sea level results in a prompt clinical improvement and, within 2 months at sea level, in return of blood gases, circulation, and respiration at rest to virtually normal values except for a slight residual pulmonary hypertension (Peñaloza *et al.*). On the other hand, the clinical picture of brisket disease is dominated by the consequences of severe pulmonary hypertension and cor pulmonale, i.e., by severe right ventricular failure, functional tricuspid insufficiency, and dependent edema of the brisket. Although the clinical pictures of seroche and brisket disease overlap some-

what, hypoxemia and polycythemia are far less striking in the animals than in man (table 4).

At least part of the severe pulmonary hypertension of brisket disease is attributable to the sphincteric construction of the small precapillary pulmonary vessels in cattle; presumably this anatomical arrangement not only affords unusual intrinsic resistance to blood flow but also effects an intense pulmonary precapillary vasoconstriction in response to mild hypoxia (199). It is not yet settled if postcapillary events (left heart failure, constriction of the pulmonary veins, or "throttles") are also involved in severe brisket disease.

Thick pulmonary precapillary vessels are also found in native residents at high altitudes. Thus, the small precapillary vessels are thicker than their counterparts at sea level and smooth muscle extends further down the pulmonary vascular tree at altitude than at sea level. This medial hypertrophy of the pulmonary precapillary vessels suggests that the pulmonary hypertension of man at altitude originates in morphologic changes as well as in vasomotor activity (Arias-Stella and Saldana, unpublished observations).

Acute Hyperoxia

Enrichment of the inspired air with oxygen, or the substitution of 100 per cent oxygen for air, is without appreciable effect on the normal pulmonary circulation (132). This lack of effect is consistent with the notion that the resistance vessels of the normal pulmonary circulation—despite the normal unsaturation of mixed venous blood—ordinarily have little "tone." On the other hand, oxygen-rich mixtures have been shown to partially relieve pulmonary hypertension of chronically hypoxic and hypoxemic animals and man (132, 164, 389). The effectiveness of oxygen-rich mixtures as pulmonary vasodilators in hypoxemic states has led to the use of oxygen-rich mixtures to relax hypertonic pulmonary vascular smooth muscle in nonhypoxemic states. However, there is no apparent reason to suspect that hyperoxia will dilate pulmonary vessels which are not hypoxemic.

Acute Hypercapnia

At first encounter, the published accounts of the effects of breathing 5 to 10 per cent CO₂ in air on the pulmonary circulation are utterly confusing. Undoubtedly, part of the confusion arises from the failure to take into account the peculiarities of the different preparations and experimental conditions. The situation is improved by sorting the results according to

TABLE 4. *Chronic Mountain Sickness in Cattle and in Man**

| | Cattle | Man |
|---------------------|----------------------------------------------|-----------------------------------------------|
| SYNONYM | BRISKET DISEASE | SEROCHE |
| Altitude | 8,000 to 12,000 ft. | >12,000 ft. |
| Prepotent mechanism | Pulmonary vasoconstriction | Severe hypoxemia and hypercapnia |
| Major consequences | Severe pulmonary hypertension; cor pulmonale | Polycythemia; moderate pulmonary hypertension |
| Clinical disability | Congestive heart failure | CNS disturbances; lassitude, fatigue, dyspnea |

* Based on observations of Hecht *et al.* (199).

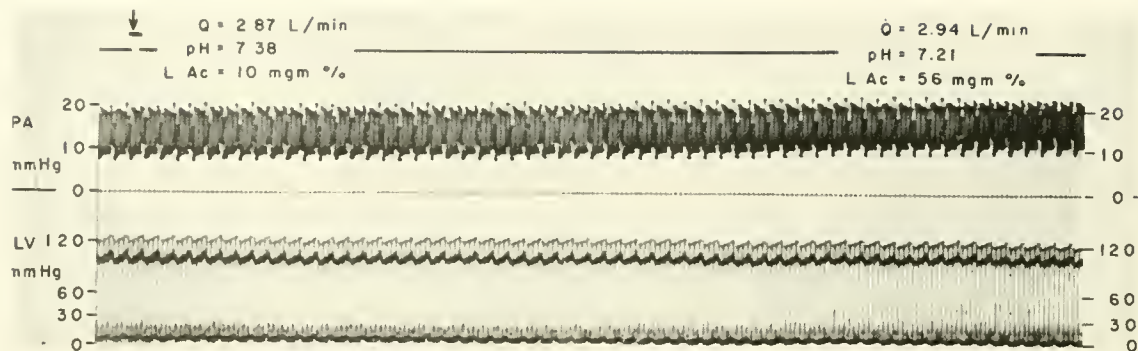


FIG. 45. A continuous record of the pulmonary arterial (PA) and left ventricular (LV) blood pressures in the dog prior to, and during, an infusion of 0.3 M lactic acid. The arrow above the pressure tracing indicates the start of the infusion. The values for cardiac output (\dot{Q}), blood pH and blood lactate concentration (L Ac) on the left were obtained during the control period; those on the right are after 3 min of the infusion. Time lines occur at 1-sec intervals; the duration of the entire record is 3 min 15 sec. [Unpublished records of Bergofsky *et al.* (24).]

four categories: isolated lungs, unilateral hypercapnia, controlled ventilation, and spontaneous ventilation (132). But, even though results tend to be consistent within each category, the differences between categories may be quite striking. Thus, in spontaneously breathing animals and man, acute hypercapnia is generally without effect on pulmonary hemodynamics (132); conversely, in anesthetized animals which are being passively ventilated, acute hypercapnia usually increases pulmonary vascular resistance (24). Recent observations have suggested a basis for this disparity: for example, during anesthesia and controlled CO_2 breathing—when the ventilatory response to inspired CO_2 is limited by the apparatus—respiratory acidosis is common; on the other hand, during spontaneous breathing—when the increase in ventilation is quite marked—respiratory acidosis is ordinarily mild. In the next section it will be shown that severe acidosis increases pulmonary vascular resistance. Accordingly, the effects of breathing CO_2 on the pulmonary circulation appear to depend on the degree of acidosis which it produces.

Acute Acidosis

For a long while, observations on the isolated lung (116, 305) and on the lungs perfused in situ (423) led to the opinion that acidosis played no role in the regulation of the pulmonary circulation. Recently, this view was challenged by experiments on similar preparations which not only indicated that acute acidosis is capable of eliciting an increase in pulmonary vascular resistance, but also suggested that it might be involved in the pulmonary vascular response

to acute hypoxia (269). That acidosis can also elicit an increase in the pulmonary vascular resistance in the intact anesthetized dog is shown in figure 45; in these animals, the pressor response seems to arise from pulmonary vasoconstriction and to depend upon the degree of acidosis rather than upon specific anions (24, 30). It should be noted that this constrictor effect of acidosis on pulmonary vascular smooth muscle stands in marked contrast to the inhibitory effects of acidosis on systemic vascular smooth muscle (402).

Another use of alkali and amine buffer has been to test the idea that acidosis may underlie the pulmonary arterial pressor response to acute hypoxia (269). This idea could not be substantiated in normal man (24). Instead, the conclusion was reached that acute hypoxia and acute acidosis constitute independent stimuli for pulmonary vasoconstriction; however, it is conceivable that in subjects with regional hypoventilation, the two separate stimuli may act synergistically to divert pulmonary blood flow to the well-ventilated portions of the lung (24).

Alveolar Hypoventilation

Alveolar hypoventilation may be uniform, as in patients with kyphoscoliosis or extreme obesity (25), or spotty, as in chronic bronchitis and emphysema. During ambient-air breathing, the designation "alveolar hypoventilation" implies a combination of alveolar hypoxia and hypercapnia; the state achieves clinical significance when sufficiently severe to produce systemic arterial hypoxemia and respiratory acidosis (138). Experimentally, it has been deliberately induced by artificial underventilation during general anesthesia (359). Largely on the basis of such experiments, it has

been claimed that alveolar hypoventilation elicits pulmonary arterial hypertension not only by way of acute hypoxia but also by an hypothetical "alveolo-vascular reflex." Since mechanical underventilation of the lungs involves an element of mechanical collapse of alveoli as well as a change in the alveolar gas composition, the operation of this special alveolar reflex is difficult to prove. Nonetheless, this hypothetical reflex is consistent with the consensus that pulmonary vasomotor effects of acute hypoxia (by airway) are independent of systemic arterial hypoxemia (204).

Pulmonary Vasomotor Reflexes

The plentiful supply of autonomic nerves to the lungs and of nerve fibers to the pulmonary blood vessels has stimulated the search for direct evidence of pulmonary reflex activity. This search has disclosed that numerous afferent vagal fibers and baroreceptor endings exist in the large pulmonary arteries, that the impulse activity of the pulmonary baroreceptor fibers varies with the pulsatile blood pressure in the pulmonary artery and that the receptors are active at the usual levels of pulmonary arterial pressure (80). On the other hand, since the efferent limbs have not yet been traced either to their conjunction with afferent limbs or to their endings in effector cells, the proof of their existence consists entirely of indirect physiologic observations, e.g., systemic vasodilation as pulmonary arterial pressure increases (6).

The pulmonary circulation is believed to participate in a wide variety of mechano- and chemoreflexes (207, 393). Some of these hypothetical reflexes are conceived to be purely local, e.g., pulmonary veno-arteriolar (6, 101, 231, 409) or alveolar-vascular (359); these local reflexes are inaccessible for direct appraisal. Much more tangible are the remote reflexes.

Three types of remote reflexes have been extensively studied. The first is a reflex from the pulmonary vessels to the systemic circulation. With rare exception (261), this type of reflex has been "depressor" in nature, evoking bradycardia and systemic arterial hypotension in response to a wide variety of stimuli; the stimuli have included an increase in static pressure at either end of the pulmonary vascular tree or along its whole length (6, 110), chemoreflexes of different kinds (99), and pulmonary vascular hypothermia (159).

The second type of remote reflex is a combined or chain reflex from the pulmonary arteries to the small pulmonary vessels on the one hand (4, 321) and to the respiratory apparatus on the other (432). With few

exceptions (101), such a reflex has customarily been invoked to account for the dramatic clinical syndrome which follows multiple pulmonary emboli, i.e., the pulmonary hypertension, the rapid shallow breathing, the bronchoconstriction, and the decrease in peripheral arterial oxygenation (227). However, many of the links in this reflex chain reaction remain speculative. More precisely defined, but much less meaningful with respect to function, are the chemoreflex pathways which connect the pulmonary arterial tree with the respiratory apparatus (99).

The third type of remote reflex runs from the reflexogenic areas of the carotid arterial bifurcations and aortic arch to the pulmonary circulation (206). To create the proper experimental setting for the demonstration of these feeble reflexes, Daly and Daly were obliged to resort to the "vasosensory controlled perfused living animal" preparation in which the pulmonary and systemic circulations could be separately controlled. In this special preparation, intense pressor stimulation of the systemic baroreceptors evoked pulmonary vasodilatation; perfusion of the carotid chemoreceptors with hypoxic or venous blood (during interrupted bronchial arterial flow) evoked pulmonary vasoconstriction (96). The authors are careful to point out that the elaborate controls required to demonstrate the existence of these reflex pathways obscure the meaning of these reflexes for the live, intact organism (95).

Pulmonary Vasomotor Waves

Rhythmic oscillations in systemic arterial blood pressure (Traube-Hering-Mayer waves) were first described toward the close of the nineteenth century (404). Although the consensus since then has favored the view that these systemic waves reflect the rhythmic activity of the medullary vasomotor center, not always has irradiation from the respiratory to the vasomotor center been excluded. Most often, the Traube-Hering-Mayer waves have been encountered in abnormal or deteriorating experimental preparations; even in the same preparation the pattern of the waves tends to vary with respect to frequency and to amplitude (229).

Infrequently, the swings in systemic arterial blood pressure were found to be associated with swings in pulmonary arterial blood pressure (125). And, on rare occasion, the pulmonary arterial swings occurred either without (379), or with barely perceptible (125), systemic arterial waves. In these few instances, other passive effects were not entirely excluded.

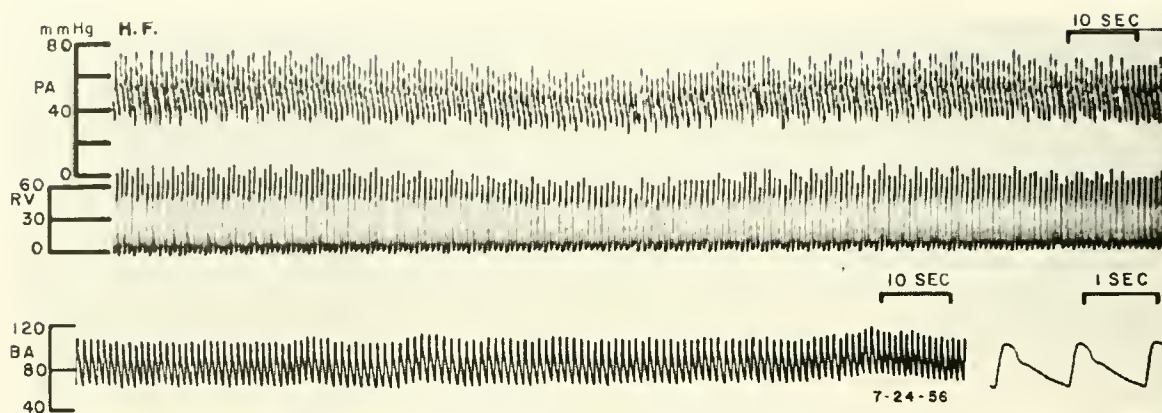


FIG. 46. Spontaneous rhythmic fluctuations in pulmonary arterial blood pressure in a young woman with primary pulmonary hypertension. The pulmonary arterial systolic pressure is identical with the systolic pressure in the right ventricle. The pulmonary arterial pressure waxes and wanes. Each cycle is 110 sec long; the pulmonary arterial systolic pressure ranges from 57 to 74 mm Hg; the diastolic pressure ranges from 26 to 36 mm. The pressure changes are not accompanied by parallel changes in heart rate. The brachial arterial pressure is somewhat low. The slow cyclic variations in pulmonary arterial pressure have no counterparts in the systemic blood pressure. (Unpublished observations by A. P. Fishman and A. G. Jameson.)

Recently, a pulmonary arterial rhythm, unaccompanied by fluctuations in systemic arterial blood pressure, was observed in an unanesthetized woman with primary pulmonary hypertension (fig. 46). In this subject, systemic hypotension coexisted with pulmonary hypertension, a combination which presumably favors the occurrence of isolated pulmonary arterial pressure waves in the experimental animal (379). However, while it is intuitively attractive to accept the pulmonary arterial waves in this subject as a manifestation of a central vasomotor rhythm—superimposed by the central nervous system on local pulmonary vascular controls—the probability remains that the fluctuations in pulmonary arterial pressure may merely reflect the passive consequences of rhythmic changes in systemic hemodynamics (125).

EFFECTS OF DRUGS

Interests in the pharmacology of the pulmonary circulation differ: at one extreme is the use of drugs to display the capacity of the pulmonary vessels to undergo a change in "tone"; this has led to the study of isolated perfused lungs and vascular rings. At the other extreme is the effect of a particular drug on the pulmonary circulation under natural conditions; this has involved the study of the unanesthetized intact animal or man in whom the ventilation, circulation, and the coordinating neurohumoral systems are all

intact. Between these extremes are many shades of interest which are not always defined or self-evident from the experimental protocols.

It is generally difficult, in intact animal and man, to separate the direct, local vasomotor effects of a drug on the pulmonary circulation from its indirect, passive effects originating from afar, i.e., in the systemic circulation, the left heart or the ventilation. Theoretically, this distinction should be easily made if the pharmacological agent, such as acetylcholine, is rapidly destroyed by contact with blood (122): minute quantities of acetylcholine are infused into a peripheral vein or into the pulmonary artery at a rate carefully adjusted to avoid the classical circulatory picture of systemic vasodilatation and cardiac inhibition; the action of the drug is then presumed to be confined to the pulmonary circulation. During this venous or pulmonary arterial titration with acetylcholine, steady-state measurements are made, not only of pulmonary blood flow and pressures, but also of other relevant respiratory and circulatory parameters (153).

Of more universal applicability is the procedure of injecting a drug into the pulmonary artery while recording blood pressures simultaneously from the pulmonary artery, the pulmonary vein (or left atrium), and a systemic artery as the drug traverses the pulmonary circulation (fig. 33) (150, 187). At first, the use of this approach required open thoracotomy for the cannulation of the pulmonary vessels

(225). However, the gradual progression from angiotomy cannulae (187) to combined right and left heart catheterization (92) has made it feasible to record simultaneously the blood pressures at both ends of the pulmonary circulation as well as the blood pressure in a systemic artery in the intact, unanesthetized animal and man.

Predominantly Passive Effects

Certain familiar drugs seem to affect the pulmonary circulation of the intact animal or man predominantly by way of the systemic circulation. Cardinal examples are the effects of digitalis and quinidine in subjects with left heart failure: digitalis reduces the pulmonary hypertension of left heart failure by improving myocardial performance; quini-

dine, on the other hand, improves the emptying of the left heart by decreasing systemic vascular resistance rather than by a direct action on the myocardium (87, 129).

The effects of epinephrine on the pulmonary circulation have long been disputed, primarily because of the occurrence of simultaneous changes in both the systemic and pulmonary circulations (97, 187, 436). However, granting that a direct pulmonary vasoconstricting effect can be demonstrated in special preparations (355), in the intact animal the increase in pulmonary arterial pressure evoked by epinephrine is almost exclusively a consequence of passive back pressure from the left heart and systemic circulation (187). Indeed, in the dog, excessively large doses of epinephrine reproduce the sequence elicited by the intracisternal implantation of fibrin (64, 372), including pulmonary hypertension and pulmonary edema from left heart failure. And, consistent with the prepotent effects of epinephrine on the systemic circulation in the dog, is the observation that in the turtle (single ventricle), intravenous epinephrine increases systemic vascular resistance without affecting pulmonary vascular resistance (443).

Levarterenol (*l*-norepinephrine) also elicits an increase in pulmonary arterial pressure. As in the case of epinephrine, the capacity for pulmonary vasoconstriction can be demonstrated by special techniques (355). However, in intact man, the increase in pulmonary arterial pressure elicited by levarterenol is predominantly, if not exclusively, passive, i.e., secondary to an increase in left atrial pressure (fig. 47) (163).

Histamine elicits a complex series of ventilatory and circulatory effects. In the isolated lung, it elicits vasoconstriction (442); the intensity of this response varies with the species, dose, and preparation. In intact man, tolerable doses, which are sufficient to elicit systemic hypotension, are without discernible effect on pulmonary hemodynamics; whether tolerable doses are inadequate to provoke pulmonary vasoconstriction, or whether vasoconstriction does occur and is neutralized by some concomitant passive effects, remains unsettled (4). Finally, the induction of severe systemic hypotension in the dog by large quantities of histamine is associated with passive pulmonary hypotension (100).

Pulmonary Vasoconstrictors

The systemic circulation is far more sensitive to the usual vasoconstrictor agents than is the pulmonary circulation. However, a host of apparently unrelated

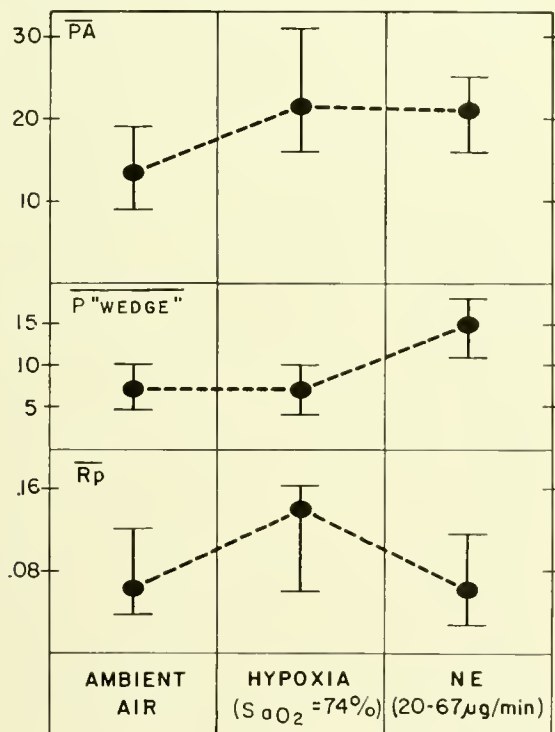


FIG. 47. Comparison of the effects of acute hypoxia and of infusing norepinephrine on pulmonary vascular pressures and resistance. \overline{PA} = mean pulmonary arterial pressure; \overline{P} "WEDGE" = mean pulmonary arterial wedge pressure; $\overline{R_p}$ = mean pulmonary vascular resistance. The solid circles represent the average values for the group of 13 normal subjects; the vertical bars represent the range. During hypoxia, the increase in pulmonary arterial pressure was not associated with an increase in "wedge" pressure; during norepinephrine infusion, an increase in pulmonary arterial pressure was invariably associated with an increase in "wedge" pressure. Accordingly, calculated resistance increased during hypoxia and decreased during norepinephrine infusion. [After Goldring *et al.* (163).]

substances have been categorized as pulmonary vasoconstrictors. These include serotonin (5-hydroxytryptamine) (34, 302, 356) adenosine triphosphate (4), small quantities of hypertonic saline (28), bacterial endotoxins (245) and alloxan (4).

Serotonin, which has captured physiological and clinical imaginations on many different accounts, is also generally held to be a uniquely effective pulmonary arterial and venous vasoconstrictor (43, 227). The evidence rests largely on animal experiments (4, 366) and on the behavior of isolated lungs (158) since "safe" doses in intact man are without discernible pulmonary vascular effect (193). At first encounter, the discrepancies between the effects of serotonin in animals and man might be attributed to a "species" difference; however, even this refuge is uncertain because of the diffuse and bizarre effects of serotonin: *a*) its tendency to produce "temporary emboli," so that an increase in pulmonary arterial pressure and an increase in pulmonary vascular resistance may arise from transient occlusion of small pulmonary vessels as well as from vasoconstriction (235), *b*) its bronchoconstricting effects (366), *c*) its respiratory and Bezold-like circulatory effects in the intact animal (193), and *d*) the discrepancies between the doses of serotonin used in the different experiments. Finally, the ineffectiveness of tolerable doses of serotonin as a pulmonary vasoconstrictor in man is consistent with the lack of pulmonary hypertension in patients with serotonin-secreting tumors (399).

Aside from their apparent proclivity for the venous side of the pulmonary circulation, these pharmacological pulmonary "vasoconstrictors" have little in common. For example, in contrast to serotonin and alloxan, endotoxin requires contact with blood to become effective (4). Moreover, hypertonic saline (333, 376), as well as serotonin, has been shown to conglutinate red cells (235). It is clear that much remains unknown about these pulmonary vasoconstrictors.

Pulmonary Vasodilators

Interest in pulmonary vasodilators has been stimulated both by the clinical need for therapeutic agents to relieve pulmonary hypertension and the physiologic concern with pulmonary vasomotor tone. Aviado (4) has sorted the substances which have been tested into five groups: 1) musculotropics (aminophylline); 2) parasympathomimetics (acetylcholine); 3) sympathomimetics (isoproterenol); 4) adrenergic blockers (tolazoline); and 5) ganglionic blockers (hexamethonium). A good number of these have been

used to treat systemic hypertension, indicating the complex hemodynamic changes which may be expected to complicate the interpretation of their effects on the pulmonary circulation. It is also noteworthy that none have yet found a place in the treatment of pulmonary hypertension, and that, except for acetylcholine, none have provided any fresh insights into the regulation of the pulmonary circulation.

Acetylcholine has achieved clinical pre-eminence as a pulmonary vasodilator. This reputation arises largely from recent experiences with pulmonary hypertensive patients since previous studies on intact animals, artificial preparations and normal man have been contradictory (132). As mentioned previously, the experiments which have adduced evidence for a pulmonary vasodilating effect of acetylcholine have exploited the rapid destruction of acetylcholine by the cholinesterases of the blood to restrict the action of acetylcholine to the pulmonary circulation (122, 401). The experiments have involved either a single injection of acetylcholine into the venous circulation or pulmonary artery (187, 192, 441), or a continuous infusion of acetylcholine into the pulmonary artery at a rate (0.5 mg/min) insufficient, at least by conventional tests, to affect either the lungs, the respiration, the left heart, or the systemic circulation (153). The evidence that acetylcholine elicits pulmonary vasodilatation includes: *a*) a decrease in the pressure gradient across the lungs in pulmonary hypertensive subjects in whom the pulmonary vessels are presumably hypertonic (192, 282, 441); *b*) a partial or complete reversal of the anticipated increase in calculated pulmonary vascular resistance during acute hypoxia (153); *c*) the prevention of the increase in unilateral resistance during unilateral hypoxia by the infusion of acetylcholine on the hypoxic side (90); and *d*) a decrease in the peripheral arterial oxygenation of patients with supposed ventilation-perfusion abnormalities (383). The last effect is generally believed to reflect the diversion of mixed venous blood to hypoventilated portions of the lungs as local hypoxic vasoconstriction is relieved by the acetylcholine; however, alternate explanations such as the opening of arteriovenous shunts or atelectasis have also been proposed. It has been indicated elsewhere that while these experiments on man are consistent with a pulmonary vasodilating effect of acetylcholine, they are not entirely convincing (132).

Other vasodilator substances and autonomic blocking agents (including spinal anesthesia) have also been used in the attempt to elicit pulmonary vaso-

dilation, especially in pulmonary hypertensive subjects (4, 369, 386). Granting that these agents are often capable of relieving pulmonary arterial hypertension, it has yet to be shown that their hypotensive effect represents pulmonary vasodilation.

GARDIOPULMONARY DISORDERS

Pulmonary Arterial Hypertension

According to the range of normal values described earlier in this chapter, pulmonary arterial hypertension exists when pulmonary arterial pressures exceed approximately 30/18 mm Hg. Even such mildly hypertensive levels have been found to strain the heart if continued for a lifetime (363). Moreover, subjects with "high-normal" pulmonary arterial pressures at rest often become pulmonary hypertensive when blood flow is increased acutely, as by occlusion of a pulmonary artery (68) or by exercise (132); the latter observations suggest that pulmonary arterial hypertension occurs frequently in the course of daily activities once pulmonary arterial pressures reach "high-normal" levels at rest.

The causes of pulmonary arterial hypertension may be conveniently sorted into four categories. Three of these are mechanical (passive): reduction in the extent and distensibility of the pulmonary vascular bed, increase in pulmonary blood flow, and increase in pulmonary venous pressure; the fourth is vasoconstriction (active). Before considering these mechanisms separately, it should be noted that pulmonary hypertension is more often the consequence of a complex interplay of mechanisms than of any single influence operating independently. Moreover, in patients with cardiopulmonary disorders, it is generally easier to single out the prepotent mechanism than to try to quantify the relative contributions of all the mechanisms that could conceivably be involved (88).

RESTRICTED VASCULAR BED. In normal animal and man, almost two-thirds of the lungs have to be removed before pulmonary arterial pressures reach hypertensive levels (89, 252). By way of contrast, there are many pulmonary diseases which surreptitiously reduce the number and caliber of small pulmonary vessels and modify the distensibility of the remaining vessels, so that even a normal pulmonary blood flow is associated with marked pulmonary hypertension. Examples of such diseases are pulmonary emboli,

pulmonary arteritis, interstitial fibrosis and granuloma, bullous emphysema, and "primary pulmonary hypertension" (341). The architecture of the thorax may also limit the capacity and expansibility of the pulmonary vascular bed: thus, in subjects with severe kyphoscoliosis, the combination of a dwarfed pulmonary vascular bed and an adult cardiac output predisposes to pulmonary hypertension (25).

INCREASE IN PULMONARY BLOOD FLOW. It has been indicated previously, that in the normal pulmonary circulation, the cardiac output has to be tripled before pulmonary hypertensive levels are reached (89). In patients with congenital cardiac defects and left-to-right shunts, pulmonary hypertension may occur even at lower blood flows because of anatomical, and possibly functional, changes in the vessels. An especially interesting situation obtains in patients in whom both the pulmonary and systemic circulations communicate, as in the reptilian heart, with the left ventricle. In this case, the partition of the left ventricular output between the two circulations is a function of their relative resistances: in time, if pulmonary vascular resistance to perfusion increases, the pulmonary blood flow will diminish even though the level of pulmonary hypertension remains unchanged (440).

INCREASE IN PULMONARY VENOUS PRESSURE. The two previous causes of pulmonary arterial hypertension are unrelated to the level of the pulmonary venous pressure. But, in the 130 years since James Hope, it has become common knowledge that pulmonary venous hypertension leads to pulmonary arterial hypertension (213). Etiologically, pulmonary arterial hypertension of this type generally originates either in mitral valvular disease or left heart failure. In dogs with acute or subacute (up to ten months) mitral stenosis, the increment in pulmonary arterial pressure appears to be a direct consequence of back pressure: as pulmonary venous pressure and pulmonary blood volume increase, the pulmonary capillary and arterial pressures also rise, but not to the same degree as the pulmonary venous pressure; since the decrease in the pressure gradient is associated with an unchanged cardiac output, the calculated pulmonary vascular resistance decreases (176). Clinical counterparts of this experimental situation are rare but do occur; they are characterized by complete restoration of the pulmonary arterial blood pressure to normal as the pulmonary venous hypertension is relieved.

The more common clinical situation is one in

which the pulmonary arterial pressure is inordinately high for the level of the pulmonary venous pressure, the pulmonary blood volume is not abnormally large, and relief of the pulmonary venous hypertension does not completely restore the pulmonary arterial pressure to normal levels. In such patients, the persistence of pulmonary arterial hypertension after relief of the back pressure is attributable to secondary effects, i.e., to anatomical changes in the lungs and vessels, possibly abetted by constriction of the small pulmonary arteries (238).

One prevalent notion about chronic pulmonary venous hypertension is that it elicits "protective" vasoconstriction of pulmonary precapillary vessels. Although it is self-evident that pulmonary arterial hypertension must occur if sufficient forward flow is to continue in the face of pulmonary venous hypertension, the teleological advantage of pulmonary precapillary vasoconstriction is not entirely clear: heightened "arteriolar" tone would increase the pressure work of the right heart and only reduce capillary blood pressure if it succeeded in reducing the pulmonary capillary blood flow. Teleologically, the prevention of undue filtration pressures in the pulmonary capillaries would be more economically accomplished by quieting the heart rather than by increasing the right ventricular work. Indeed, the inability to resolve the question of protective vasoconstriction again emphasizes that pulmonary vasomotor activity is exceedingly difficult to recognize in the abnormal pulmonary circulation, particularly when structural changes have extended beyond the vessels into the surrounding lung.

PULMONARY ARTERIAL VASOCONSTRICTION. In normal dog, cat, and man, pulmonary arterial vasoconstriction rarely evokes more than a mild pulmonary hypertension. On the other hand, in cattle, contraction of the sphincteric pulmonary arterioles often effects dramatic increases in pulmonary arterial pressure (199). This correlation between vascular structure and the intensity of the pulmonary vascular response raises the prospect that pulmonary vascular disease may, by thickening vascular media, enable the small muscular vessels to contract with unusual vigor. However, this ingenious notion has yet to be critically tested (181).

Cor Pulmonale

Pulmonary hypertension attracts clinical attention when it causes the right heart to enlarge (dilate or

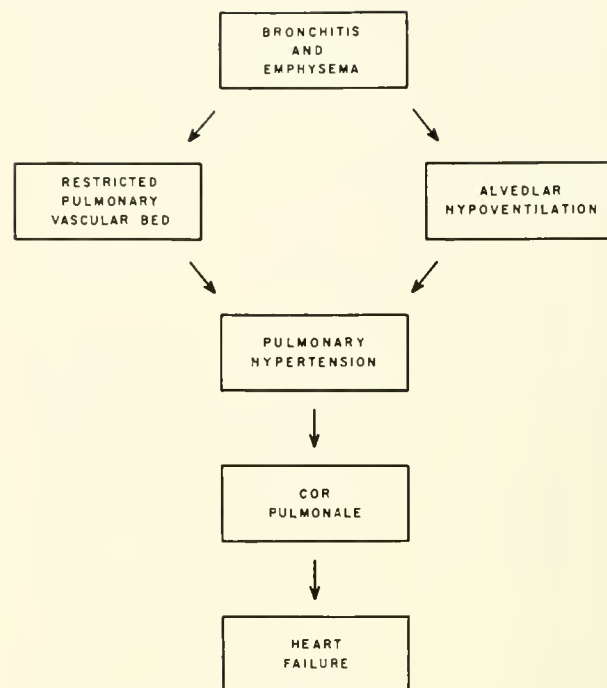


FIG. 48. The evolution of cor pulmonale and right heart failure in chronic pulmonary emphysema. Alveolar hypoventilation contributes to pulmonary hypertension by way of hypoxia and respiratory acidosis: hypoxia elicits pulmonary vasoconstriction, polycythemia, hypervolemia, increased blood viscosity, and increased cardiac output; acidosis elicits pulmonary vasoconstriction.

hypertrophy) or to fail. The term *cor pulmonale* is generally reserved for right ventricular enlargement which originates either in diffuse pulmonary disease or in ineffective performance of the chest bellows. As a rule, pulmonary hypertension underlies *cor pulmonale*; in some types of lung disease, particularly those associated with hypoxemia, the abnormal pressure work of the right heart may be supplemented by an abnormally high cardiac output, i.e., flow work (89, 339, 341).

It has become clear that the genesis of *cor pulmonale* is to be sought in the mechanisms which ordinarily determine the normal pulmonary arterial pressure; only the combinations and the prepotent influences differ. For example, in diffuse interstitial diseases of the lung (e.g., "alveolar-capillary block") anatomic changes in pulmonary vessels and parenchyma operate without benefit of increased flow or hypoxia. On the other hand, in the concentric alveolar hypoventilation of extreme obesity, respiratory paralysis or kyphoscoliosis, hypoxia and respiratory acidosis elicit pulmonary hypertension in subjects with normal lungs. Finally, in the most common

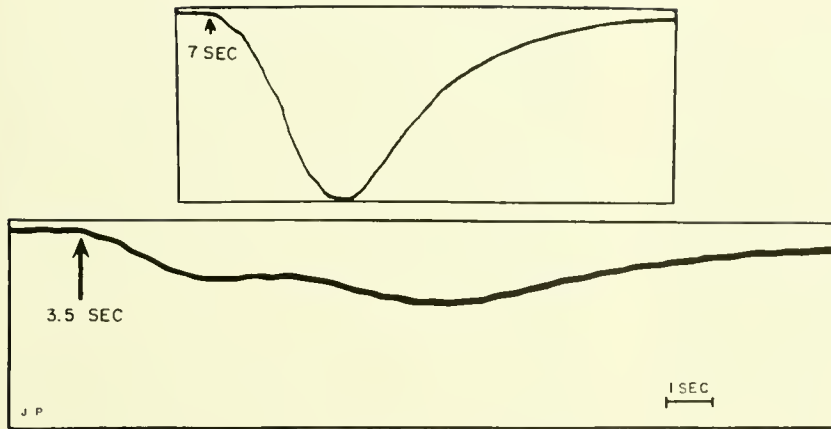


FIG. 49. Dye-dilution curve inscribed by densitometer from peripheral artery following injection of Evan's blue dye (T-1824) into the pulmonary artery. The upper curve is normal. The short appearance time and abnormal initial deflection of the lower curve are characteristic of pulmonary arteriovenous shunts.

cause of cor pulmonale, i.e., chronic bronchitis and emphysema, a combination of anatomic changes, hypoxia and acidosis are involved: destruction of alveolar capillaries sets the stage by restricting the pulmonary vascular bed, generally without evoking pulmonary hypertension; the picture is completed by disturbances of alveolar ventilation and perfusion—usually incidental to an acute bronchitis—which superimpose the vasoconstriction of hypoxia and respiratory acidosis on the structural changes (fig. 48) (341).

It is clinically and physiologically important to recognize the occurrence of right heart failure in patients with cor pulmonale. Prior to heart failure, the enlarged right ventricle functions normally: it is filled by an atrial inflow pressure of a few mm Hg, it

empties approximately half of its volume during each ejection and it increases its output during exercise in accord with metabolic requirements. The first signs of right ventricular failure generally appear during exercise: as ventricular emptying is compromised, the mean filling pressure increases to abnormal levels (7–10 mm Hg) and the increase in cardiac output is no longer commensurate with the increase in oxygen uptake (341).

Pulmonary Edema

In 1878, Welch produced pulmonary edema in rabbits by either ligating the aorta or compressing the left ventricle. He attributed the pulmonary edema to the pulmonary congestion and pulmonary venous

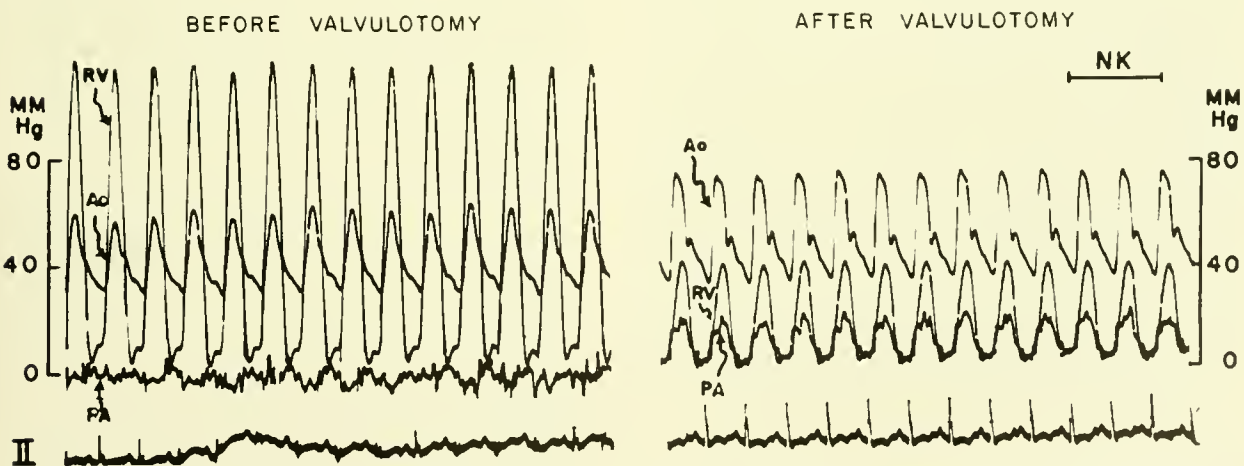


FIG. 50. Blood pressures recorded during open thoracotomy in a patient with pulmonic stenosis. *Before valvulotomy.* Marked right ventricular hypertension coexists with systemic hypotension. The pulmonary arterial pressure pulse is vibratory. *After valvulotomy.* The right ventricular pulmonary hypertension has been considerably relieved. The pulmonary arterial pressure has increased and the pressure pulse is characteristic of pulmonic insufficiency. [After Himmelstein, *et al.* (210).]

hypertension which followed the induced (transient) imbalance between the outputs of the two ventricles (411).

Since then, many other experimental procedures have been used to produce pulmonary edema: vagotomy, vagal stimulation, intravenous infusion of fluid, left heart failure, increase in intracranial pressure, exhibition of epinephrine, and exhibition of ammonium chloride (411). These share a common denominator: an excessively high pulmonary venous and capillary pressure. Accordingly, they are consistent with Welch's hypothesis; and, the origin of the pulmonary edema which these procedures effect is to be regarded in the light of Starling's law of transcapillary exchange (174).

It would be misleading to imply that an inordinate filtration pressure in the pulmonary capillaries underlies all types of experimental and clinical pulmonary edema. For example, the pulmonary edema caused by α -naphthylthiourea does seem to depend on an increase in capillary permeability (114); an increase in capillary permeability has also been postulated to account for the bilateral pulmonary edema which follows the injection of a starch suspension into a lobar pulmonary artery (227). However, continued emphasis on hemodynamic balances promises to be rewarding for several reasons: *a*) the usual forms of pulmonary edema do seem explicable in terms of the usual determinants of transcapillary exchange of water, solutes, and colloids, i.e., in terms of Starling's law (174, 385, 411); *b*) many earlier types of so-called "neurogenic" pulmonary edema disappeared when subjected to analysis in terms of conventional hemodynamic parameters (64, 372); *c*) uncertainties as to the precise mechanisms involved in special types of pulmonary edema are bound to prevail until elusive parameters, such as capillary pressure, volume, and permeability on the one hand, and the role of the lymphatics on the other, can be precisely measured and defined in quantitative terms (325); and *d*) mysterious influences should only be given credence when the local hemodynamic and physicochemical mechanisms operating across capillary walls have been taken into full account, and found wanting (217).

Pulmonary Hypotension

During bleeding to the point of systemic arterial hypotension as well as during traumatic and histamine shock, the circulating blood volume, the cardiac output, and the central venous pressures

decrease (100, 289, 391). However, despite the progressive decline in systemic arterial and left atrial blood pressures, the pulmonary arterial pressure tends to stabilize at approximately two-thirds of its initial value. This stability presumably involves the gradual closure of portions of the pulmonary vascular tree as intraluminal pressures in these areas fall. As a result of the preferential closure of certain portions of the pulmonary vascular tree during systemic hypotension, the affected portions of the lungs become excessively ventilated for their perfusion, leading to an appreciable arterial-alveolar difference in carbon dioxide tension (of the order of 8 mm Hg) and to the creation of an "alveolar dead space." Restoration of the circulating blood volume raises the pulmonary arterial pressure to supracontrol values even though slight systemic arterial hypotension persists (160).

Pulmonary Arteriovenous Fistula

The surgical production of a pulmonary arteriovenous anastomosis is associated with a decrease in systemic arterial oxygenation and in pulmonary arterial (mean) pressure. The subsequent course of the experimental animal, as well as the natural history of the human subject with a pulmonary arteriovenous fistula (155), is determined by the size of the shunt and the degree of systemic arterial hypoxemia which it effects. If systemic hypoxemia is sufficiently marked, a considerable polycythemia will ensue leading, in turn, to an increase in the viscosity of the blood, an increase in the resistance to blood flow through the usual resistance vessels and the diversion of more and more of the right ventricular output through the low-resistance shunt (fig. 49).

Pulmonic Stenosis

A hindrance to the exit of blood from the right ventricle occurs commonly as a congenital cardiac malformation; either the valve or the infundibulum or the main pulmonary artery may be the seat of the stenosis. Experimentally, stenosis of the pulmonary artery has been produced in different ways (12). In all, severe narrowing of the lesion is necessary before the right ventricle becomes strained.

In the absence of an abnormally large blood flow across the pulmonary valve, the physiologic hallmark of pulmonic stenosis is right ventricular hypertension coupled with a systolic blood pressure gradient between the right ventricle and pulmonary artery (fig. 50). In acute animal experiments, a constriction

of the pulmonary arterial lumen of at least 40 per cent is needed to raise systolic pressure appreciably in the right ventricle; greater degrees of constriction are needed to produce right ventricular failure, i.e., dilatation of the right heart, abnormally high end-diastolic pressures in the right ventricle, and tricuspid regurgitation (12). Parenthetically, it may be noted that pulmonic stenosis is an excellent physiological tool for stimulating the proliferation of the pulmonary collateral arterial circulation (263, 264).

Pulmonary Valvular Insufficiency

Pulmonary valvular insufficiency has been produced experimentally in dogs (123) and during remedial cardiac surgery in man (fig. 50). After avulsion of the valve, not only does the pulmonary arterial diastolic pressure fall to right-ventricular

diastolic levels, but a systolic right ventricular-pulmonary arterial pressure gradient may also appear. This gradient is a consequence of unusually rapid and turbulent flow during systole rather than of pulmonic stenosis (123).

Pulmonic insufficiency is generally regarded as a benign lesion: in dogs, performance on the treadmill as well as end-diastolic pressures in the right ventricle remains normal after months of exercise and despite right ventricular systolic pressures approximating 100 mm Hg (12). However, pulmonic insufficiency may bring the heart closer to the brink of its reserve so that an additional lesion, e.g., tricuspid insufficiency may precipitate overt heart failure (12). Whether the cardiac reserve is sufficient to tolerate pulmonary valvular insufficiency for a lifetime, or only for a few years, remains to be established.

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